On the cognitive and neuronal effects and mechanisms of working memory training

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To my grandmother

Hilja Salminen

(1918-2014)

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ABSTRACT

Working memory (WM) is a cognitive function that is engaged in several everyday tasks. WM performance predicts performance in diverse other cognitive functions. Additionally, WM decline at old age is associated with age-related impairments in others cognitive functions, thus affecting autonomous performance of everyday tasks. It has been shown that WM can be improved with training interventions, and evidence has accumulated showing that also other cognitive functions can profit from WM training. The transfer findings indicate that WM training might enclose a mechanism to improve cognitive functions in general. Even though there exists a growing body of evidence on the possibilities to improve cognitive functions with WM training in different populations, the exact mechanisms of training and transfer have remained unclear. In the current dissertation I examine the prospects and precise mechanisms of WM training with four studies using the bi-modal dual n-back paradigm. I showed that dual *n*-back training improved performance in various tests tapping executive functions. I could also demonstrate that the mechanisms underlying transfer result from an improvement in a specific process tapped by the training task rather than in the boosting of a general cognitive ability. Consequently, transfer can occur to tasks if they engage the same specific process. Additionally, I provided primary evidence that only 16 sessions of WM training produces microstructural changes in white matter pathways connecting brain regions that support WM functions. I also showed for the first time that age-related differences in WM performance between young and older adults can be compensated for after only 16 training sessions. The findings of the present dissertation are discussed in relation to the flexibility of cognitive functions and the plasticity of the underlying neuronal substrate; additionally, new conceptions to models of training and transfer mechanisms are presented.

Keywords: working memory, cognitive training, fMRI, DTI

ZUSAMMENFASSUNG

Die Kapazität des Arbeitsgedächtnisses (AG) sagt die Leistungsfähigkeit in diversen anderen kognitiven Funktionen voraus. Zusätzlich werden altersbedingte Beeinträchtigungen in AG mit Defiziten in anderen kognitiven Funktionen assoziiert, was sich im hohen Alter in der Minderung der Selbständigkeit und des Leistungsniveaus in alltäglichen Aufgaben widerspiegelt. Das AG kann durch Trainingsmaßnahmen verbessert werden, und auch andere kognitive Funktionen können von AG-Training profitieren. Die Befundlage bezüglich dieser Transfereffekte deutet darauf hin, dass AG-Training auch Mechanismen zur Verbesserung der allgemeinen kognitiven Leistungsfähigkeit umfasst. Obwohl es zunehmend Hinweise für die Möglichkeit gibt, kognitive Funktionen durch AG-Training zu verbessern, sind die genauen Mechanismen von Training und Transfer noch unklar. In der vorliegenden Dissertation präsentiere ich vier Studien, in denen ich die genauen Mechanismen von AG-Training untersucht habe. Ich konnte zeigen, dass Training die Leistung in verschiedenen Tests zu exekutiven Funktionen verbessert, und dass der Transfer von Trainingseffekten statt auf die Förderung einer allgemeinen kognitiven Fähigkeit auf die Verbesserung in einem spezifischen Prozess zurückzuführen ist. Weiterhin habe ich zum ersten Mal gezeigt, dass bereits 16 Sitzungen eines AG-Trainings zu strukturellen Veränderungen in der weißen Substanz führen. Diese ließen sich in den Nervenbahnen nachweisen, die die mit AG assoziierten Hirnareale verbinden. Ich zeigte erstmals auch, dass altersbedingte Unterschiede in AG zwischen jungen und älteren Erwachsenen bereits nach 16 Trainingssitzungen ausgeglichen werden können. Die Befunde der vorliegenden Arbeit werden in Bezug auf die Flexibilität der kognitiven Funktionen und auf die Plastizität des zugrunde liegenden neuronalen Substrats diskutiert. Zusätzlich werden neue Ansichten für Modelle von Training- und Transfermechanismen vorgestellt.

Stichwörter: Arbeitsgedächtnis, kognitives Training, fMRI, DTI

LIST OF ORIGINAL STUDIES

This dissertation is based on the following research articles:

I. Salminen T., Strobach, T., & Schubert, T. (2012). On the impacts of working memory training on executive functioning. *Frontiers in Human Neuroscience, 6*(166).

II. Salminen, T., Kühn, S., Frensch, P. & Schubert, T. (submitted). Transfer after dual *n*-back training depends on striatal activation change.

III. Salminen, T., Mårtensson, J., Kühn, S., & Schubert, T. (2016). Increased integrity of white matter pathways after dual *n*-back training. *NeuroImage, 133*, 244-250.

IV. Salminen, T., Frensch, P., Strobach, T., & Schubert, T. (2016). Age-specific differences of dual *n*-back training. *Aging, Neuropsychology, and Cognitio*n*, 23*(1), 18-39.

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INTRODUCTION

"*Train your brain in minutes a day!*", "*Brain training changes your capacity to think and learn!*", "*Train the brain - get smarter!*", "*Turn your struggling student into a successful student!*"

These promises of different brain training programs demonstrate how much the appeal of brain training that has greatly increased in the last decade. Not only has this happened because of more developed technical devices that are now generally accessible, but also because studies published in the last decade have shown that different cognitive functions can indeed be improved by training. Previously it was firmly believed that cognitive abilities reach their peak at around 25-30 years of age. Now many programs promise to break any boundary to cognitive capacities that one has been born with. Surrounded by different brain training approaches one is confronted with questions concerning the flexibility of the boundaries of our cognitive functions. What can be trained? When do improvements derived from training transfer to untrained tasks and functions? Does training change the structure of the brain? Can cognitive training be used to resist cognitive decline? In this dissertation I will shed more light onto these open issues relative to one of our most fundamental cognitive functions, working memory (WM).

Why WM? It is a limited-capacity system that contains short-term storages for auditory and visual information and a central executive that updates and manipulates the storage contents (Baddeley, 1986; Baddeley & Della Sala, 1996; Baddeley & Hitch, 1974). WM capacity predicts performance in several other tasks ranging from simple attentional tasks (Bleckley, Durso, Crutchfield, Engle, & Khanna, 2003; Fukuda & Vogel, 2009; Kane, Bleckley, Conway, & Engle, 2001) to tasks tapping more complex abilities, such as reading comprehension (Daneman & Carpenter, 1980), reasoning and problem solving (Barrouillet & Lecas, 1999; Engle, Carullo, & Collins, 1991; Engle, Kane, & Tuholski, 1999; Fry & Hale, 1996; Kyllonen & Christal, 1990), and executive functioning in everyday life (Kane et al., 2007). Therefore, WM plays a central role among other cognitive functions. WM is susceptible to aging, and cognitive impairments in the elderly can partly be attributed to a decline in WM (Hertzog, Dixon, Hultsch, & MacDonald, 2003; Verhaeghen & Salthouse, 1997).

Considering the dependency of several other cognitive functions on WM processes as well as the fundamental role that WM plays in daily life and throughout the life span, it is clear that elucidating the further possibilities for and more precise mechanisms of WM training is of great importance. Even though training interventions which target WM and attempt to improve untrained functions in the process have become especially popular recently, there are still open questions concerning the potentials and mechanisms of WM training. I have approached these questions in the present dissertation with four studies. The WM training paradigm in all studies was the dual *n*-back task, which will be described in detail at a later point.

In my first study I investigated the scope and characteristics of untrained cognitive functions that may benefit from dual *n*-back training. I especially focused on executive control functions. In the second study I assessed the mechanisms of transfer from dual *n*-back training. This goal was realized by measuring training-related functional changes in the underlying neuronal substrate with functional magnetic resonance imaging (fMRI). In my third study I analyzed the training-related plasticity of the neurostructural connections between brain regions related to WM. This data was gathered by applying the diffusion tensor imaging (DTI) method in MRI. Finally, in the fourth study I investigated to what extent age-related cognitive decline can be compensated for by WM training, and for this I analyzed dual *n*-back training and transfer effects in older adults. The specific research questions of the four studies thus were:

1. Do WM training effects from dual *n*-back training transfer to executive functions?
2. What are the mechanisms of transfer to untrained tasks?
3. Does training produce changes in the neurostructural connections between brain regions that support WM processes?
4. What are the dual *n*-back training effects and transfer effects to executive functions in older adults?

In the following I will first describe the theoretical and methodological framework for my dissertation, followed by the empirical part in which each study is presented in detail. Finally, in the general discussion the results from the four studies will be recapitulated and implications for training literature and future directions will be presented.

In early WM training studies participants had to learn a new strategy to improve their performance in a given task (Butterfield, Wambold, & Belmont, 1973; Ericsson, Chase, & Faloon, 1980). This meant, for example, instructing the participants to form chunks of the presented items for better retention (instead of "4-7-7-6-2-9" one memorizes "477-629"). Although such *strategy-based* training improved performance in the trained task, the improvements did not transfer to untrained tasks with new stimuli, and thus the intervention's external validity was low. In contrast to strategy-based training, positive results concerning transfer effects have come from studies using *process-based* training paradigms (Schubert, Strobach, & Karbach, 2014). Such training is designed to improve cognitive processes generally without providing the participant with explicit strategies for successful task performance.

In addition to aiming at improving a cognitive process (instead of a strategy) by the training intervention, another essential characteristic of effective training paradigms is task adaptivity. This means that the difficulty level of the training task should be constantly adjusted according to the performance of the participant. The idea of task adaptivity is based on the framework by Lövdén, Bäckman, Lindenberger, Schaefer, and Schmiedek (2010). It formulates that changes in the cognitive system are triggered by "the capacity for reacting to a mismatch between supply and demand" (p. 662). Such a mismatch means on one hand that the current neuronal substrate is not sufficiently equipped to perform the task and therefore it must be altered through functional and anatomical changes. On the other hand, a mismatch may also mean that the task demands are lower than the neuronal substrate is equipped to process, and thus, neuronal structures are altered to unload redundant substrate. The training task should therefore not be too difficult or too easy. This objective can be achieved through task adaptivity: improved performance can be reached by adjusting the level of difficulty to match the boundaries of the participant's performance, under which the task is too easy and above which it would be too difficult. Such task adaptivity provokes the expansion of performance borders.

A further critical characteristic for training success is training time. Previous studies have shown that the most efficient training schedules consist of at least three weeks or eight

hours of training (Klingberg, 2010). Here it should also be considered that massed practice has been shown to be less effective than spaced practice (Cepeda, Vul, Rohrer, Wixted, & Pashler, 2008; Wang, Zhou, & Shah, 2014). That is, eight hours of training spanning over several days or weeks yields stronger effects than eight hours of training on one single day. Put together, the most efficient training interventions consist of process-based adaptive training spanning a broad time period.

DUAL *N*-BACK TRAINING PARADIGM

In the studies of the current dissertation I used a bi-modal dual *n*-back training paradigm (from now on: dual *n*-back[1]). In an *n*-back task the participant has to respond to a stimulus whenever it matches a stimulus presented *n* steps back (Kirchner, 1958). For example, in a 2-back task a response is required when the currently presented stimulus is the same (in identity, location, feature, etc.) as the one presented two stimuli back. The task difficulty increases as a function of load, so that a 3-back task is more demanding than a 2-back task (Braver et al., 1997; Jonides et al., 1997). The dual *n*-back (Figure 1) engages auditory and visual WM processes simultaneously by including independent but co-occurring auditory-verbal (AV) and visuospatial (VS) *n*-back tasks (Buschkuehl, Jaeggi, Kobel, & Perrig, 2007; Jaeggi et al., 2003). This way the task is unique in nature, as it entails a WM component and a dual-task component, thus engaging additional cognitive processes that are required in the coordination of multiple simultaneous tasks (Strobach, Salminen, Karbach, & Schubert, 2014).

Hence, the dual *n*-back taps several important cognitive functions: updating of items in WM, inhibition of old or irrelevant items, and coordination of the performance of simultaneous tasks (Jonides et al., 1997). These separate functions – WM updating, inhibition, and task

[1] In the current dissertation the term "dual *n*-back" stands specifically for the bi-modal dual *n*-back task. A few studies have used other variations of a dual *n*-back task, such as a dual-process *n*-back task (e.g., Takeuchi et al., 2010). However, in those cases the tasks were presented only in one modality (in contrast to the two modalities in the bi-modal dual *n*-back). The bi-modality of the dual *n*-back is an essential characteristic of the task; this is outlined in the main text. It is crucial to recognize this distinction from other types of dual *n*-back tasks.

coordination skills – can generally be classified as executive control functions (Baddeley, 1996; Emerson, Miyake, & Rettinger, 1999; Miyake et al., 2000). They are necessary in diverse everyday tasks such as reading, mental calculation, and planning future events; that is, they include processes that are readily applied on a daily basis. Furthermore, dual *n*-back performance correlates with measures of fluid intelligence (Jaeggi, Studer-Luethi, et al., 2010), which indicates that it might reflect the capacity of some general cognitive ability.

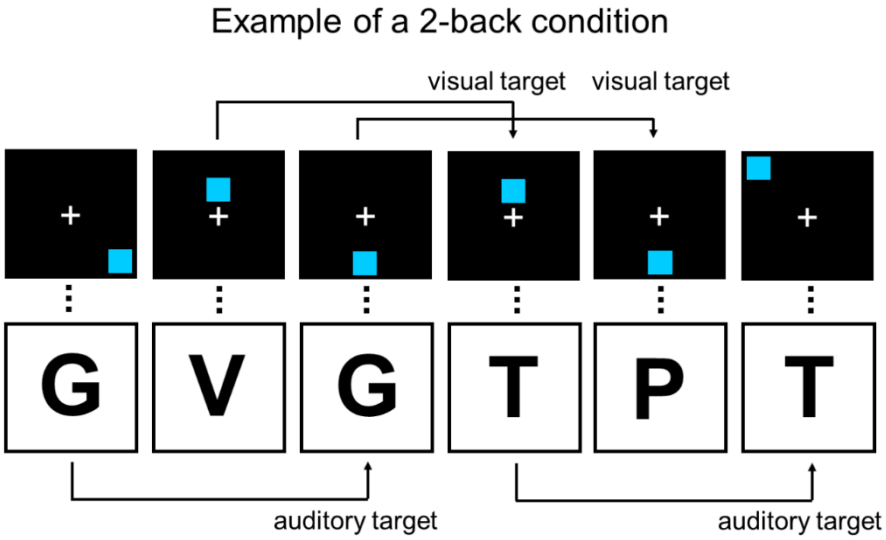

Figure 1. Example of a 2-back condition in the dual *n*-back task (adapted from Buschkuehl et al., 2007). The visual and auditory stimuli are presented simultaneously at identical rates.

The inclusion of two modalities plays a special role in the complexity of the dual *n*-back. Rarely are we in everyday tasks required to integrate auditory and visual information so that they are given an equal weight. Instead information from one modality is sufficient with the other modality providing support. The two modalities can actually distract each other when presented simultaneously but independently of each other. For example, when one reads a newspaper and listens to the radio at the same time it is fairly difficult to conceive both sources equally. Indeed, Jaeggi et al. (2003) showed that performance in the dual *n*-back task is poorer than in the single subtasks, as measured in reaction times and accuracy.

Performance in the dual *n*-back can be improved with training. Several studies have shown that over a training period of approximately 20 days, trainees show an increase in performance from about 2- or 3-back to about 4- or 5-back (Anguera et al., 2012; Chooi & Thompson, 2012; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Jaeggi, Studer-Luethi, et al., 2010; Redick et al., 2013; Thompson et al., 2013). Note that the *n*-back level is always equal in the AV and the VS task, and in order to progress to the next level, the participant has to produce a certain percentage of correct responses in *both* modalities. This should encourage the participants to truly concentrate on both tasks simultaneously instead of concentrating on only one subtask while neglecting the other. Therefore it is highly likely that, in addition to WM, dual *n*-back training improves processes related to task-coordination skills and attention.

TRANSFER EFFECTS FROM WORKING MEMORY TRAINING TO UNTRAINED COGNITIVE FUNCTIONS

As elaborated in the beginning of the previous section, although WM training improved performance in the trained task, early training studies did not produce transfer effects to untrained tasks with untrained stimuli. For example, Ericsson et al. (1980) showed that their participant could increase his WM span (i.e., how many items he could maintain in and recall from his WM) from 7 to 80 digits over the course of 20 months of training. However, when tested with letters (instead of digits), his WM span dropped back to baseline. Thus, there was no transfer from trained to untrained stimuli. Transfer effects can be considered as reflecting stimulus- and task-independent improvements in cognitive functions.

Improvements after adaptive process-based WM training often transfer to other, untrained WM tasks with untrained stimuli (von Bastian & Oberauer, 2013). Notably, there exists nowadays evidence that WM training can improve performance also in cognitive functions beyond WM. For example, several studies have shown improvements after WM training in the ability to inhibit inappropriate responses as measured by the Stroop task (Chein & Morrison, 2010; Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002a, 2002b; Olesen, Westerberg, & Klingberg, 2004). Other studies have shown transfer effects from WM training to auditory and visual attention (Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009; Vogt et al., 2009; Westerberg et al., 2007) and reading comprehension (Chein & Morrison, 2010; Karbach, Strobach, & Schubert, 2015). Improvements in mathematical/arithmetic abilities in different participant groups have also frequently been reported (Holmes, Gathercole, & Dunning, 2009; Takeuchi et al., 2011; Van der Molen, Van Luit, Van der Molen, Klugkist, & Jongmans, 2010). Transfer effects to non-verbal reasoning have been observed in healthy adults (Olesen et al., 2004) as well as in children with attention deficit hyperactivity disorder (Klingberg et al., 2005; Klingberg et al., 2002b), but these effects have proven to be difficult to replicate (Chein & Morrison, 2010; Dahlin, Nyberg, Bäckman, & Stigsdotter Neely, 2008; Holmes et al., 2009; Takeuchi et al., 2011; Thorell et al., 2009; Van der Molen et al., 2010; Westerberg et al., 2007).

As for transfer effects from dual *n*-back training, Jaeggi et al. (2008) reported in a seminal study about transfer to fluid intelligence. Participants were divided into groups of 8-, 12-, 17-, and 19-days of dual *n*-back training, and it was revealed that both training and transfer effects were associated with the amount of training: the longer the training time, the larger the training and transfer effects. The transfer effect from dual *n*-back training to fluid intelligence tests has been replicated in some studies (Jaeggi, Studer-Luethi, et al., 2010; Stephenson & Halpern, 2013), whereas others have questioned its validity (Chooi & Thompson, 2012; Redick et al., 2013; Thompson et al., 2013). Although being controversial, the findings by Jaeggi et al. (2008) spurred the idea that dual *n*-back training might improve some general cognitive ability. This idea is supported by other studies that have shown transfer effects from dual *n*-back training to attention (Lilienthal, Tamez, Shelton, Myerson, & Hale, 2013) and spatial visualization abilities (Stephenson & Halpern, 2013).

Redick et al. (2013) tested transfer effects from dual *n*-back training to a battery of 17 tasks measuring different cognitive functions (e.g., multitasking, crystallized intelligence, fluid intelligence, perceptual speed) and they did not find any transfer. Although these results could be regarded as not very encouraging concerning the efficiency of dual *n*-back training, they are in strong contrast with other studies that have shown transfer. The results of Redick et al. (2013) should be interpreted with some caution due to certain methodological issues. For example, Schmeichel (2007) has shown that administration of several consecutive tasks on executive control causes mental fatigue that impairs the participants' performance in further tasks (see also Persson, Welsh, Jonides, & Reuter-Lorenz, 2007). It might be that the extensive battery of transfer tests applied by Redick et al. (2013) was too exhaustive for the participants, and thus had a confounding role in the results (for detailed discussions, see Green, Strobach, & Schubert, 2014; Schubert & Strobach, 2012). Furthermore, the training curve in the study by Redick et al. (2013) was shallower than the one reported for example in Jaeggi et al. (2008). This implies that the participants in Redick et al. (2013) did not improve as much as in Jaeggi et al. (2008); a factor that also might have reduced transfer. Jaeggi, Buschkuehl, Shah, and Jonides (2014) note that the magnitude of the improvement in the training task should be considered when comparing transfer effects between studies.

All things considered it is still unclear to what extent dual *n*-back training improves untrained cognitive functions. I conducted Study 1 to investigate whether dual *n*-back training effects transfer to those executive control functions that the dual *n*-back is assumed to tap on (as described in the previous section). In contrast to Redick et al. (2013), the battery of tests was limited in order to restrict the effects of mental fatigue. Also, the test battery was systematized largely based on a prominent model on executive functions by Miyake et al. (2000). I expected that if dual *n*-back training effects extend to those executive functions that it engages, there would be improvements (i.e. transfer effects) in tasks tapping on those functions. Alternatively there might not be any transfer as in Redick et al. (2013), which would imply that the training effects are rather restricted.

WORKING MEMORY TRAINING EFFECTS ON THE NEURONAL SUBSTRATE

Studying behavioural transfer effects brings insight into the range of cognitive processes that may be improved by training. However, just as it is important to reveal *what* is transferred, it is also important to analyse *when and how* it is transferred. One way to look at the mechanisms of transfer is to assess neuronal activation patterns and training-related changes in them by means of neuroimaging (Jonides, 2004). The advantage of using neuroimaging methods over measuring sole behavioural changes is that neuronal measures can reveal commonalities between the training and transfer tasks that may not be apparent on the behavioural level, for example in situations in which transfer occurs between tasks that share only little or no overlap between the engaged cognitive processes. Neurofunctional measures can reveal common activation components that clarify how transfer occurred.

Neurostructural measures on the other hand, can reveal microstructural changes that are informative about the plasticity of the structural connectivity of the neuronal substrate that is affected in training. Structural connectivity of the brain plays a crucial role in cognitive performance (Nagy, Westerberg, & Klingberg, 2004), and therefore analyzing training-related changes in these connections is of high interest with regard to elucidating the factors that underlie improved performance after training.

In the following I first delineate the neurofunctional basis of WM. As microstructural changes in the living human brain can with the current methods be assessed only across a longer time scale than a single imaging session would allow, the structural connections related to WM will be described in the section concerning longitudinal training-related structural changes. Following the neurofunctional correlates of WM I present methods of how to assess training-related changes on a neurofunctional and –structural level. Afterwards, previous findings of training-related changes in the neuronal substrate are presented (neurofunctional and neurostructural), along with a description of the motivations for Studies 2 and 3.

NEURONAL CORRELATES OF WORKING MEMORY

Studies have shown that WM tasks activate a neuronal network comprising areas in the bilateral prefrontal and parietal cortices, the bilateral premotor cortex, and the bilateral anterior cingulate (D'Esposito et al., 1995; D'Esposito, Postle, & Rypma, 2000; Mottaghy, 2006; Smith & Jonides, 1998). The WM activations in the frontoparietal regions (Figure 2, left) overlap with activation patterns observed in several different cognitive tasks, for which reason this network is often referred to as the *general*, *amodal*, or *associative* frontoparietal network (Duncan & Owen, 2000; Niendam et al., 2012; Tamber-Rosenau, Dux, Tombu, Asplund, & Marois, 2013; Zanto & Gazzaley, 2013).

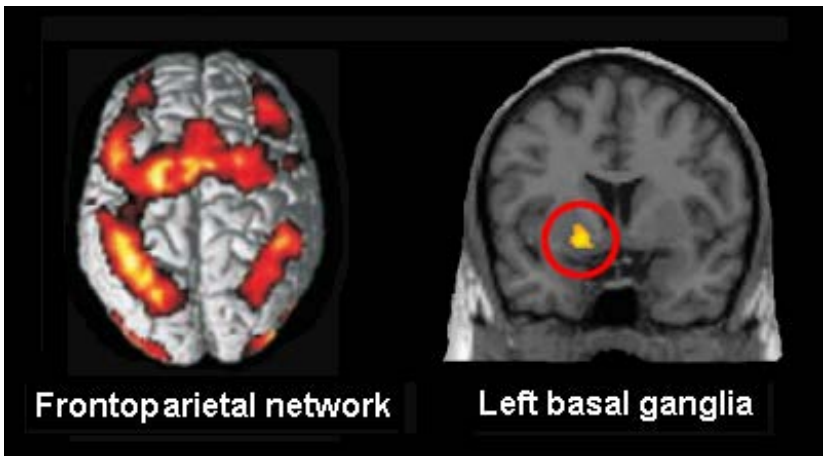

Figure 2. Neuronal activation in working memory tasks. (Left) **T**he frontoparietal network including the bilateral prefrontal and parietal cortices as well as the bilateral premotor cortex (adapted from Dahlin, Stigsdotter Neely et al., 2008). (Right) The basal ganglia showing activation in the left striatum (adapted from McNab and Klingberg, 2008).

Additionally regions in the basal ganglia are involved in the updating function of WM, serving as a gate controlling the input of items into WM (Alexander, DeLong, & Strick, 1986; Baier et al., 2010; Frank, Loughry, & O'Reilly, 2001; Gruber, Dayan, Gutkin, & Solla, 2006; Voytek & Knight, 2010) (Figure 2, right). It has been suggested that the striatum especially plays a crucial role in the gating function of WM updating processes, that is, in regulating which information is allowed to enter WM. This is assumed to happen via the dopaminergic system of the frontostriatal neuronal pathways that controls information input to WM by modulating neuronal

activations in the prefrontal cortex (PFC) (Cohen, Braver, & Brown, 2002; McNab & Klingberg, 2008; O'Reilly, 2006).

As for the neuronal correlates of the *n*-back task, Jaeggi et al. (2003) studied neuronal activations in single and dual *n*-back tasks in three different load conditions: 1-, 2-, and 3-back. At the highest load condition (3-back), both single and dual *n*-back tasks activated a wide network of brain regions, including the bilateral dorsolateral prefrontal cortex (dlPFC), the bilateral inferior frontal gyrus, the bilateral superior parietal lobule, the bilateral precentral gyrus, and the left supplementary motor cortex; that is, several regions in the generally observed WM network. At all load conditions, the bilateral superior parietal lobule showed activation in both the single and the dual *n*-back task. However, at all load conditions, only the dual *n*-back (and not the single *n*-back) produced activation of the left precentral gyrus and the right dlPFC, and in two out of three load conditions in the dual *n*-back task an activation of the left dlPFC and the bilateral inferior frontal gyrus was shown. These dual *n*-back specific activations in the dlPFC presumably represent the dual-task component of the dual *n*-back, because this region has previously been shown to be activated in dual-task processes (Schubert & Szameitat, 2003; Stelzel, Kraft, Brandt, & Schubert, 2008; Szameitat, Schubert, Müller, & von Cramon, 2002). Jaeggi et al. (2003) showed that activation in the neuronal *n*-back network increased as a function of load whereas the participants' performance became poorer (measured in accuracy and reaction times). This pattern indicates that the more demanding the task becomes (e.g. increasing load from 2-back to 3-back), the stronger is the neuronal response.

HOW TO MEASURE TRAINING-RELATED NEURONAL CHANGES?

Longitudinal training studies rely on pretest – posttest –designs, in which measurements (of behavioral performance, neuronal functions, brain structure, etc.) are first conducted before training in order to assess the baseline level, and subsequently the same measurements are conducted after training. Comparisons between the two time points indicate changes that have taken place during training. To exclude the possibility that structural changes, for example, reflect only effects of normal maturation, the results of the training group are contrasted to those of a control group that has not undergone any training (passive control group) and / or to those

of a control group that has trained on another task that involves processes which can be dissociated from the trained processes of interest (active control group).

Functional magnetic resonance imaging (fMRI) allows for assessment of the level of deoxygenated blood in the brain and subsequently produces an estimate of the brain regions that showed activation during a specific task. This is based on the assumption that neuronal activation consumes oxygen, so the acquired blood-oxygen-level dependent (BOLD) signal provides an indirect measure of brain activity. The advantage of fMRI over other functional neuroimaging methods, such as positron emission tomography (PET) is that the image resolution in fMRI is relatively high, with measurements possible in as small volume elements (voxels) as three cubic millimeters. This allows more specific estimations of the locations of neuronal activity. Additionally in contrast to PET, fMRI is non-invasive as no contrast agent is required.

Diffusion tensor imaging (DTI) provides a method to investigate brain structure *in vivo* by measuring the magnitude and direction of water diffusion in the brain. The amount of water diffusion varies according to restricting barriers, such as fibers and membranes so, that diffusion is greater along tissue boundaries than against them. In DTI, after measuring the magnitude of water diffusion at each voxel, a diffusion tensor model is fitted to the measurements. This produces parameters that can be used to analyze the quantity and direction of diffusion, and the neuronal tracts that connect different brain regions can be depicted (Johansen-Berg & Rushworth, 2009; Zatorre, Fields, & Johansen-Berg, 2012). A commonly assessed parameter is fractional anisotropy (FA), which estimates the directional dependency of diffusion. When diffusion is *isotropic* it is equal in all directions; *anisotropic* diffusion again is greater along one axis than other directions. FA values close to 0 reflect isotropic (unrestricted) diffusion, whereas FA values close to 1 reflect anisotropic (restricted) diffusion. Therefore, larger FA values can be considered to mirror higher white matter integrity than smaller FA values. DTI provides more reliable estimates of structural connectivity within the brain than other structural measures (based on T1-weighted MRI) because it does not require predefined regions for analysis but can be performed on a whole-brain level. Additionally, methods based on the measurement of T1 signal can provide information on the volume of white matter tissue, but not on the axonal

directions and consequently the connections between brain regions, which can be inferred from DTI.

NEUROFUNCTIONAL CHANGES AFTER WORKING MEMORY TRAINING

Studies that have associated WM performance and neuronal functions in different developmental stages through the lifespan are suggestive of what kind of activation changes could be expected for improved WM performance after training. First, increase of WM capacity in childhood is accompanied by an activation increase in the frontoparietal WM network (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Klingberg, 2006). Second, WM decline at old age is associated with decreased activation in the PFC as compared with young adults (Rypma & D'Esposito, 2000). These findings suggest from a developmental point of view that better performance is associated with increased activation. However, the picture does not seem to be so clear-cut. In adolescents *increased* activation in the prefrontal and inferior parietal regions as a function of improved WM performance are accompanied with *decreased* activation in superior parietal regions (Schweinsburg, Nagel, & Tapert, 2005). Also in the elderly such re-organization of brain activations has been frequently observed, such that as activation decreases in some regions, it increases in others (Persson & Nyberg, 2006; Rajah & D'Esposito, 2005). This kind of scaffolding of neuronal activations has been defined as "…the use and development of complementary, alternative neuronal circuits to achieve a particular cognitive goal" (Park & Reuter-Lorenz, 2009). Therefore a pattern of both increased and decreased activation following WM training could be expected.

One can detect three general patterns of activation changes in training literature: *increases* of neuronal activation, *decreases* of neuronal activation, or *a combination of decreases and increases* of neuronal activations; all patterns can be interpreted to reflect different mechanisms of training (Buschkuehl, Jaeggi, & Jonides, 2012; A. M. C. Kelly & Garavan, 2004; Poldrack, 2000). In one of the earliest studies investigating WM training-related neuronal changes, Olesen et al. (2004) showed an activation increase in the frontoparietal network as well as in the striatum and thalamus after five weeks of visuospatial WM training. Training-related activation increase in the WM network has since been reported also in other

WM training studies (Jolles, Grol, Van Buchem, Rombouts, & Crone, 2010; Westerberg & Klingberg, 2007). Increased activation with improved performance most likely reflects training-related strengthening of those neuronal responses that are required for successful task performance. On the other hand, some studies have shown that activation decreases in the frontoparietal network after training (Hempel et al., 2004; Schneiders, Opitz, Krick, & Mecklinger, 2011; Schneiders et al., 2012). Training-related activation decrease with improved performance could be interpreted as more efficient processing so that after training, the neuronal substrate is equipped with more capacity for other tasks.

Finally, Dahlin, Stigsdotter Neely, Larsson, Bäckman, and Nyberg (2008) observed after WM training a mixture of activation decreases and increases. They reported an activation decrease in the frontoparietal network accompanied by an increase in the striatum after five weeks of visual WM updating training (see also Kühn et al., 2013). Thus all components of the WM network were involved (frontoparietal regions and the striatum), but they showed differing effects. Such a combination of increases and decreases might reflect more efficient general cognitive processes (reflected as a decrease in the general frontoparietal network) with the processing focus having shifted to a region underlying some task-specific function (reflected as an increase in the striatum, which is associated with WM updating processes).

Considering all these findings there seems to be a wide distribution of results of WM training on neuronal activity. Although my main focus in Study 2 was to analyze training-related neurofunctional changes in order to assess the mechanisms of transfer from training, the findings from that study are intriguing also regarding neurofunctional changes after dual *n*-back training, as these have not yet been studied (mechanisms of transfer will be approached in the next chapter). As already mentioned earlier, Jaeggi et al. (2003) observed increased activation with increasing *n*-back load in the dual *n*-back task. However, their participants were not trained and the participants' performance deteriorated as the *n*-back load increased. In dual *n*-back *training* performance should improve before proceeding to the next load. Therefore the predictions of training-related activation changes cannot as such be based on the findings of Jaeggi et al. (2003). Rather, based on the findings from the aforementioned previous training

studies, diverse predictions can be made with regard to changes in neuronal activation patterns after dual *n*-back training.

First, activation could increase in the brain regions that are activated by the dual *n*-back task. As an activation increase with improved performance could be interpreted as an intensification of the neuronal signals in regions that are associated with the engaged processes, increase should be seen in WM regions, such as the frontoparietal WM network and in the striatum, as in Olesen et al. (2004). Additionally, activation should increase in the specific dual-task related frontal regions such as the dlPFC (Jaeggi et al., 2003; Schubert & Szameitat, 2003; Szameitat et al., 2002). Second, activation could decrease after training in the brain regions associated with the dual *n*-back. Since less activity is needed for a better performance, this would suggest that dual *n*-back training has produced more efficient employment of the neuronal substrate that is activated in the dual *n*-back task. Finally, dual *n*-back training could result in a mixture of decreases and increases. Based on the findings by Dahlin, Stigsdotter Neely, et al. (2008), a strong candidate pattern would be a decrease in the frontoparietal network and an increase in the striatum. Decreased activation in the frontoparietal network would imply that less general cognitive processes are required in better task performance, whereas activation increase in the striatum (which is associated with WM updating processes) would reflect increased involvement of task-specific updating processes required in the dual *n*-back. On the other hand, with the involvement of the specific dual-task function in the dual *n*-back, increased activation in brain regions related to dual-task processes could be anticipated.

NEUROSTRUCTURAL CHANGES AFTER WORKING MEMORY TRAINING

Can we make conclusions about the brain's plasticity on the basis of neurofunctional findings? According to the framework by Lövdén, Bäckman, et al. (2010), plasticity should be dissociated from flexibility. Whereas *flexibility* refers to changes that occur in existing neuronal structures, *plasticity* denotes actual structural changes due to increasing task demands. Therefore, the abovementioned changes in neuronal functions are rather descriptive of the brain's flexibility than of plasticity as a response to training. In order to draw conclusions about plasticity, one should investigate training-related structural changes. Specifically structural connectivity of the

brain is related to cognitive performance (Nagy et al., 2004), and investigating training-related changes in the structural connections between brain regions can provide important insight into the capacity for performance changes.

Also here training-related changes can be anticipated on the basis of studies that have associated WM performance with microstructural measures (Johansen-Berg, 2010). For example, in children and adolescents, better WM performance is associated with increased FA values within frontal and parietal areas as well as in the anterior part (genu) of the corpus callosum that connects the left and right PFC (Klingberg, 2006; Nagy et al., 2004; Olesen, Nagy, Westerberg, & Klingberg, 2003). Short et al. (2013) associated visuospatial WM performance in infants with FA values in major white matter tracts connecting brain regions that are related with WM functions. They found that better WM scores were associated with increased FA in the genu of corpus callosum, the arcuate fasciculi, the anterior cingulum, and the thalamocortical radiations. According to the atlas by Catani and Thiebaut de Schotten (2008) the arcuate fasciculi connect the temporal and parietal lobes to the frontal lobe, the anterior cingulum connects the anterior frontal lobe to the parietal lobe, and the thalamocortical radiations are part of the internal capsule connecting the thalamus to different parts of the cortex (Figure 3).

Thus, WM performance in infants can be predicted by the integrity of white matter microstructure in connections between the brain regions that support WM functions. In older adults the opposite pattern has been observed: impaired WM is accompanied by decreased FA values within the frontoparietal network (Moseley, 2002; Sexton, Kalu, Filippini, Mackay, & Ebmeier, 2011). Charlton, Barrick, Lawes, Markus, and Morris (2010) studied the role of FA decrease in white matter connections between cortical regions supporting WM in adults with impaired WM. They found that impaired WM performance was associated with decreased FA in temporo-parietal, temporo-frontal and fronto-parietal white matter pathways. The association between WM performance and white matter microstructure thus seems quite straightforward: increased white matter integrity in connections between brain regions that support WM functions advocates better WM. The question therefore is, whether changes after relatively short-term training interventions mirror the observed lifelong changes in white matter.

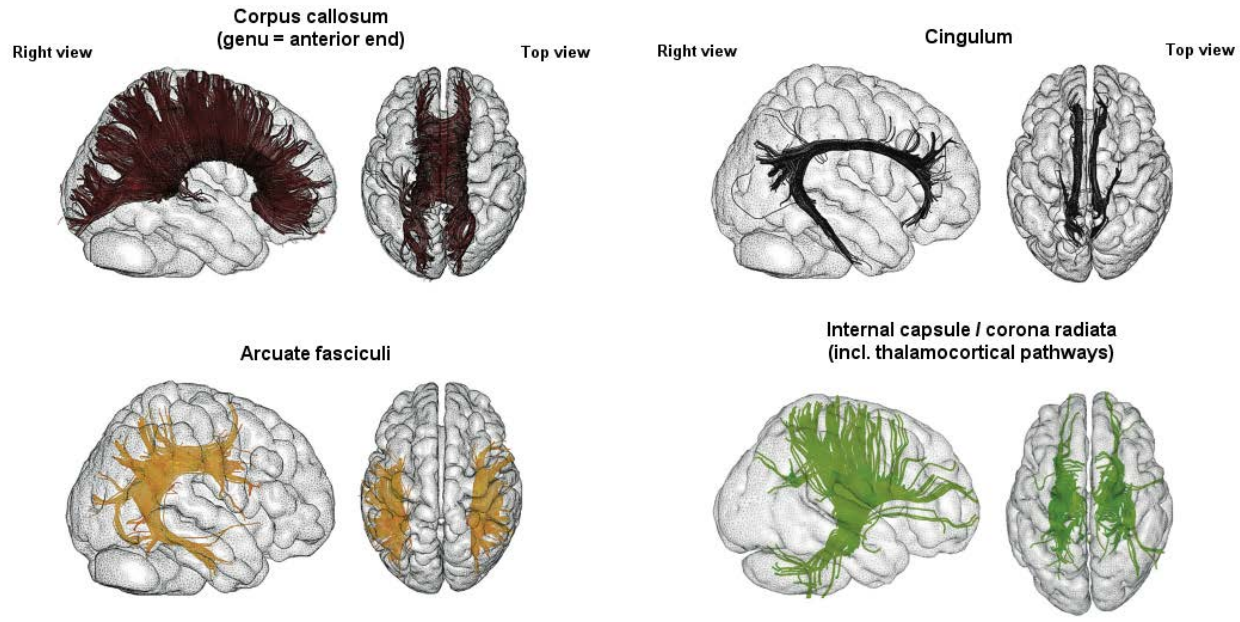

Figure 3. Pathways in which white matter microstructure has been associated WM performance in different developmental stages (adapted from Catani and Thiebaut de Schotten, 2008). The corpus callosum (top left) connects left and right hemispheres, the anterior end (genu) connects the left and right frontal lobes; the cingulum (top right) connects the frontal, parietal occipital, and temporal lobes; the arcuate fasciculi (bottom left) connect the parietal and temporal lobes to the frontal lobe; the internal capsule / corona radiata (bottom right) contain the thalamocortical pathways that connect the thalamus to different parts of the cortex.

Studies on white matter changes after WM training have been scarce. Lövdén, Bodammer, et al. (2010) studied microstructural white matter changes in young and older adults after a cognitive training intervention of 101 days, and they found increased FA after training in both age groups in the genu of corpus callosum. However, their training intervention included in addition to WM training also training of episodic memory and perceptual speed, and therefore conclusions about the effects of sole WM training cannot be made. Furthermore, they restricted their analyses to the corpus callosum, so that effects beyond this region and on a whole-brain level remained undetermined.

Only one study so far has investigated longitudinal changes after pure WM training. In their pioneering study, Takeuchi et al. (2010) showed that dual-process visual *n*-back training increased FA values in white matter regions bordering on the parietal cortex as well as in the genu of corpus callosum. Both of these regions are associated with WM. Due to the lack of a

control group it is difficult to conclude from that study to what extent the observed changes were related to training and not only reflecting natural maturation over time. However, the authors observed a correlation between improved WM performance and FA increase in the parietal node, which implies that the changes were related to training. There was no relation between improved WM performance and FA increase in the genu of corpus callosum. The authors speculated that this lack of correlation was due to a dissociation between auditory and visual WM, and that their task involved only visual WM. It has been shown that a visual WM task produces stronger activation in regions in the parietal cortex than auditory WM tasks, which again have been shown to activate regions in the PFC (Crottaz-Herbette, Anagnoson, & Menon, 2004).

Training-related changes in white matter microstructure thus seem to be manifested as increased FA in the brain regions that are involved in the respective tasks during training. This observation is in accordance with training results from other domains. For example, in a seminal study Scholz, Klein, Behrens, and Johansen-Berg (2009) found after juggling training increased FA near the intraparietal and parieto-occipital sulci, which are associated with visuo-motor integration and grasping movements. Taubert et al. (2010) however found decreased FA after whole-body balancing training in prefrontal regions. The authors recognized that the training-related decrease in FA, which contradicts with other training studies that have shown increased FA after training, is likely due to their FA changes having been found in crossing neuronal fibers in which the directionality of diffusion is difficult to determine reliably. Increased FA would therefore be the more likely and reliable pattern of change after training than decreased FA.

I looked into the changes in structural white matter connectivity after dual *n*-back training in Study 3. Dual *n*-back training could be expected to produce increased FA in white matter pathways between cortical regions related to WM. According to previous studies, the pathways include (labelled according to Catani & Thiebaut de Schotten, 2008) connections between the left and right frontal lobes (the genu of corpus callosum), connections from the parietal and temporal lobes to the frontal lobe (the arcuate fasciculi), connections from the temporal lobes to the frontal lobes (the anterior cingulum), and thalamocortical white matter pathways.

The bi-modal dual *n*-back training paradigm is likely to produce broader changes than the single-modality training paradigm in Takeuchi et al. (2010), especially in the frontal cortex. This is because previous studies have shown that the resource pools for auditory and visual information in the PFC are separate also in dual-task situations (Bayliss, Jarrold, Gunn, & Baddeley, 2003; Oberauer, Lange, & Engle, 2004). Furthermore, multimodal integration has been located in the PFC (Baddeley & Della Sala, 1996; Miller & Cohen, 2001). Analogous to the bi-modal motor training task in Scholz et al. (2009) (visual and motor) that produced pronounced FA increases in regions associated with visuo-motor integration, by activating the auditory and visual modality simultaneously one could expect stronger involvement of neuronal structures associated with multimodal integration than with a single-modality task.

PRECONDITIONS FOR TRANSFER TO UNTRAINED FUNCTIONS

Studying the preconditions for transfer is of high relevance with regard to determining the critical components of efficient training interventions. One can mainly distinguish two different transfer mechanisms that have both received support in training literature.

According to the *general boosting hypothesis*, transfer occurs when the training task boosts the domain-general frontoparietal neuronal network. Then performance should improve also in any other task that relies on the same network. For example, Klingberg et al. (2005, 2002b) suggested that this mechanism underlay their transfer effects. They studied WM training and transfer effects in children with ADHD, and transfer from training was found to untrained measures of reasoning, cognitive control, and attention. The authors referred to previous neuroimaging studies that had shown that the functions engaged by their training and transfer tasks rely on largely overlapping regions in the frontoparietal network (e.g. Duncan et al., 2000; Gray, Chabris, & Braver, 2003; Klingberg et al., 2002a; Klingberg, Kawashima, & Roland, 1996), and therefore transfer occurred (Figure 4).

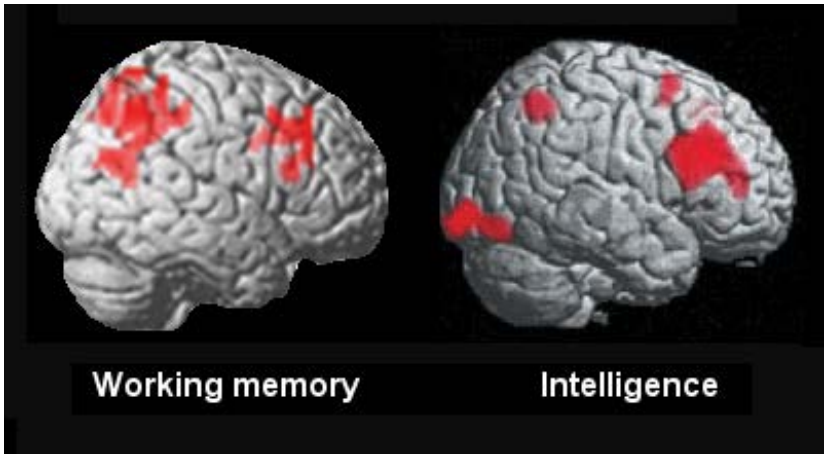

Figure 4. Activation of the general frontoparietal network (left) in a working memory task and (right) in an intelligence test (left figure adapted from Olesen et al., 2004; right figure adapted from Duncan et al., 2000). According to the general boosting hypothesis, working memory training boosts the functions of the frontoparietal network, and subsequently enhances performance in other tests (such as intelligence tests) that rely on the same network.

However, Klingberg et al. (2005, 2002b) assessed only cognitive performance changes, and therefore the neuronal basis for transfer remained speculative. Instead, Olesen et al. (2004) assessed training-related neurofunctional changes. They showed improvements after WM training in untrained tests of WM, response inhibition, as well as reasoning, and these improvements were accompanied by increased activity in the frontoparietal network. Olesen et al. (2004) suggested that the training-related boosted function of the prefrontal association cortex mediated transfer from training to the untrained cognitive tasks. It should be noted here that although "boosted function" of the neuronal substrate is generally shown as *decreased* activation with better performance (see previous chapter), Olesen et al. (2004) interpreted their *increased* activation with better performance as reflecting improved function of the underlying neuronal regions.

The alternative hypothesis, the *specific process-improvements hypothesis,* suggests that transfer occurs only when the training and the transfer task share a specific cognitive process. For example, Dahlin, Stigsdotter Neely, et al. (2008) showed transfer from WM updating training to an *n*-back task but not to a Stroop task. The authors speculated that a training-related improvement in WM updating processes enabled transfer to the *n*-back task that also includes WM updating but not to the Stroop task in which WM updating is not a dominant process. Furthermore Dahlin, Stigsdotter Neely, et al. (2008) observed that all three tasks activated overlapping regions in the frontoparietal network but only the trained WM updating task and the transfer *n*-back task activated striatal regions, while during the Stroop-task there was no activation observed in this area (Figure 5). As postulated by WM theories, the striatum is associated with WM updating processes (McNab & Klingberg, 2008). This pattern of results led to the conclusion that overlapping activations in the frontoparietal network are not sufficient for transfer effects, but it is critical that the tasks engage common processes and recruit a specific brain region that is associated with this specific process.

Dahlin, Stigsdotter Neely, et al. (2008) provided rather strong evidence to support the specific process-improvements hypothesis. However, it cannot be excluded that a training task that activates the frontoparietal network stronger than the task used in Dahlin, Stigsdotter Neely, et al. (2008) could boost the frontoparietal network more efficiently. Such a training task, like

the dual *n*-back, could produce a strong enough boost in the frontoparietal network to release capacities in this network for improved performance in untrained tasks and functions that rely on overlapping regions in the same network. Such a boost could explain for example the findings by Jaeggi et al. (2008, 2010) who showed transfer from dual *n*-back training to reasoning tests: the two measures do not seem to share a specific cognitive function but they rely on overlapping regions in the frontoparietal network.

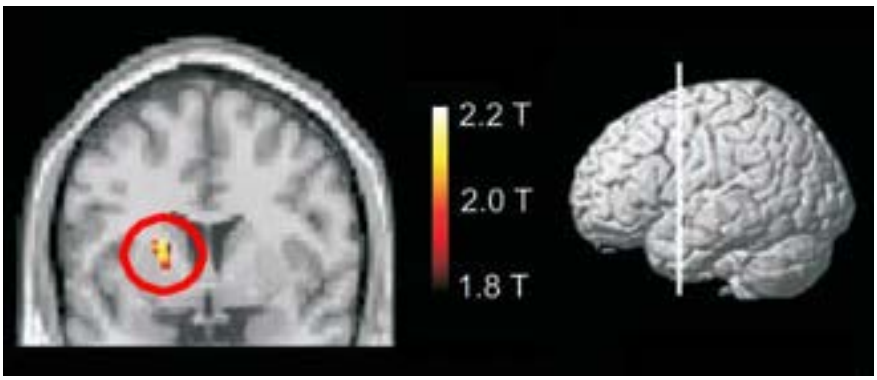

Figure 5. Striatal region that showed increased activation after WM updating training (adapted from Dahlin, Stigsdotter Neely, et al., 2008). According to the specific process-improvements hypothesis a training-related improvement in a specific cognitive process, such as working memory updating, transfers to another task that also involves that specific process. The training-related improvement is reflected as increased activation in a brain regions that is associated with that process, such as the striatum which is associated with working memory updating processes.

In Study 2 I systematically tested the two alternative hypotheses in order to answer the question, what training-related neurofunctional mechanisms mediate transfer effects? According to the two main lines of theories either (a) transfer occurs when the tasks activate overlapping regions in the general frontoparietal network, or (b) transfer occurs when the tasks engage the same cognitive process and recruit a brain region that is specific to that process. If (a) is true, I would expect transfer effects to a variety of tasks that deviate with varying degrees from the dual *n*-back but that also share some common components with the task, and activation overlap in the frontoparietal network should be predictive of transfer effects. However, if (b) is true, then I would expect transfer only to the task that shares a specific processing component

with the training task, and an activation increase in a specific brain region that is associated with that process.

TRAIN IN ORDER TO SUSTAIN: PROSPECTS OF WORKING MEMORY TRAINING IN OLDER ADULTS

The ultimate goal of WM training is undoubtedly to improve the quality of life of individuals with impaired cognitive functions, manifested as limited abilities in performing daily chores. Older adults are one population with WM impairments occurring by cause of ageing. WM training might therefore be a suitable tool in alleviating cognitive decline in these individuals and, consequently, improve their quality of life. For this reason it is highly relevant to study the potentials of WM training beyond young, healthy adults.

Indeed, in recent years a large number of studies have investigated the possibilities to compensate for age-related decline by training interventions (for reviews, see M. E. Kelly et al., 2014; Lustig, Shah, Seidler, & Reuter-Lorenz, 2009). Although earliest studies on cognitive training with older adults originate from a few decades ago (Baltes & Willis, 1982; Labouvie-Vief & Gonda, 1976), only with the development of process-based training paradigms have the true capacities for cognitive improvements through training become tangible.

Until now studies have produced variable effects of WM training in older adults. For example, Dahlin, Nyberg, et al. (2008) reported improvements only in the training task but no transfer to untrained tasks, whereas other studies have shown improvements after training also in untrained WM tasks (Buschkuehl et al., 2008; S.-C. Li et al., 2008). Some have even reported training-related improvements in untrained functions other than WM, including fluid intelligence, attention, processing speed, and episodic memory (Borella, Carretti, Riboldi, & De Beni, 2010; Brehmer, Westerberg, & Bäckman, 2012; Heinzel et al., 2014; Richmond, Morrison, Chein, & Olson, 2011).

These results are promising in showing at least some advantage of WM training interventions at an older age. Still, due to the varying extent of transfer effects, there is clearly no consensus yet on what type of a WM training paradigm is most suitable for the aging brain. Concerning the aspect of compensating for age-related cognitive decline, it could be useful to target the specific processes in which older adults deviate from young adults. From this perspective the dual *n*-back training paradigm might be an optimal candidate for targeting age-

related decline in WM. This is because it has been shown that performance differences between young and older adults increase with task complexity, and they are especially pronounced in dual-task situations when compared with single-tasks (Salthouse, 1992; Voelcker-Rehage, Stronge, & Alberts, 2006). As previous training studies with older adults have exclusively used single-modality (auditory or visual) training paradigms, dual *n*-back training would bring new insights into the age-related training literature.

As a matter of fact, Jaeggi, Schmid, Buschkuehl, and Perrig (2009) showed that also in *n*-back tasks the dual-modality version inflates performance differences between young and older adults, compared to single-modality versions. There are no studies as yet on dual *n*-back training with older adults. In Study 4 I therefore investigated what are the training effects and transfer effects to executive functions after dual *n*-back training in older adults? I expected the training and transfer effects in older adults to mirror the ones observed in Study 1 with young adults. On one hand, on the basis of previous WM training studies that have compared effects between young and older adults, it could be expected that the training and transfer results in older adults are not as strong and extensive as in young adults. On the other hand, the complexity of the dual *n*-back training paradigm could prompt broad effects in older adults, as it specifically taps on executive control processes that are markedly impaired in older adults when compared with young adults.

EMPIRICAL STUDIES

Next I will present the empirical part of the dissertation. It comprises four studies, and for each study the background, methods, and results will be described, followed by a discussion.

STUDY 1: TRANSFER EFFECTS FROM DUAL *N*-BACK TRAINING TO EXECUTIVE FUNCTIONS

Salminen T., Strobach, T., & Schubert, T. (2012). On the impacts of working memory training on executive functioning. *Frontiers in Human Neuroscience, 6*(166).

Introduction

In this study I investigated whether dual *n*-back training effects transfer to different aspects of executive functions. Previous studies have already shown transfer effects from dual *n*-back training to different cognitive functions, such as attention and fluid reasoning (Jaeggi et al., 2008; Lilienthal et al., 2013). Transfer to executive functions could be expected, considering that the dual *n*-back task engages processes that are classified as executive control functions: WM updating, control of attention between items in WM, inhibition of irrelevant items, and coordination of two simultaneous tasks. Moreover, WM predicts performance in executive functions (Baddeley & Della Sala, 1996), and therefore as WM improves with training, improvements in untrained executive functions could be anticipated. Based partly on the framework by Miyake et al. (2000), I specified four executive functions that correspond to the components of the dual *n*-back: WM updating, dual task coordination, task switching, and attentional control of items in WM.

First, the *n*-back task engages updating processes, and therefore I expected dual *n*-back training effects to transfer to an untrained WM updating task. Another study showed an improvement in visual *n*-back after visual updating training (Dahlin, Stigsdotter Neely, et al., 2008). Accordingly, a transfer effect to WM updating after dual *n*-back training could be expected. Second, I anticipated a transfer effect to dual-task performance. The dual *n*-back involves two concurrent *n*-back tasks and thus requires dual-task coordination processes. A training-related improvement in these processes could possibly manifest as improved performance also in a dual-task paradigm. Third, the dual *n*-back calls for rapid switching between the two task streams and thus it is likely to engage task switching processes. Accordingly, I expected a transfer effect to a task-switching paradigm. Fourth, dual *n*-back

training effects could be expected to transfer to attentional control processes. As new, relevant items enter WM, the old, irrelevant items have to be discarded. Simultaneously the temporal order of the items in WM has to be controlled for. All these processes engage attentional control processes; and so transfer from dual *n*-back training could be expected. Attentional control processes were assessed with the attentional blink (AB) paradigm. Finally, I tested whether participants improved after dual *n*-back training in a test on fluid intelligence. The findings concerning transfer effects from dual *n*-back training to fluid intelligence have been contradictory, with some studies showing transfer (Jaeggi et al., 2008, 2010) and others that have not (Redick et al., 2013). Thus, there is still no consensus on this issue.

Method

Twenty participants (mean age 24.4 years, five male) trained on the dual *n*-back task over a time period of three weeks. The training intervention consisted of 14 training sessions à 30 minutes. Before and after the training period the participants performed tests on the four executive functions as well as fluid intelligence. In order to dissociate retest effects from training-related improvements, a passive control group completed the same tasks with three weeks of no training between the pre- and posttests.

Transfer to WM updating was measured with a task based on the letter memory task in Miyake et al. (2000) presented as a single auditory-verbal (AV) task, a single visuospatial (VS) task, and as a dual-modality task in which the AV and VS stimuli were presented simultaneously. In this task stimulus sequences of different lengths were presented, and at the end of each sequence the last four items had to be reported; in the dual-modality task participants were randomly asked to report either the AV or the VS stimulus sequence. The dependent variable (DV) was the number of correctly reported sequences in each version of the task.

Dual-task coordination processes were assessed with a crossmodal dual-task of the psychological refractory period (PRP) type including auditory and visual stimuli (Pashler, 1994; Schubert, 1999). The participants had to respond first to the auditory stimulus and then to the visual stimulus as fast and as correctly as possible. The temporal interval between the two tasks varied randomly between the trials. A general finding is that while response to the first task is

unaffected by the interval, the speed and accuracy of the second response suffer from very short intervals. In this task the DVs were the reaction times (RTs) and error rates of responses to the second task.

Task switching was assessed with a task based on the paradigm by Rogers and Monsell (1995). All stimuli were visual. The task contained single-task trials, in which only one task had to be performed, and mixed trials, in which two tasks had to be performed. In mixed trials either the same task repeated from one trial to the next (repetition trials) or there was a task switch (switch trials). Comparisons of RTs in different trial types reflect different cognitive processes (Meiran, Chorev, & Sapir, 2000). Comparing RTs between switch and repetition trials gives an estimate of switching costs, which reflect true task switching processes. Comparison of RTs between repetition and single-task trials gives an estimate of mixing costs, which reflect sustained control processes. Here the DVs were the RTs in each trial type.

Attentional control processes were measured with a crossmodal attentional blink (AB) paradigm. It consisted of simultaneously presented rapid visual and auditory presentation streams of letters (Raymond, Shapiro, & Arnell, 1992). In each stream there were also two digits presented, separated by either a short or a long temporal interval (lag), and the participant's task was to report the first visual and the second auditory digit. The AB theory predicts that the detection of the second target (T2) is impaired when the lag between the two targets is short. Therefore, the DV of interest was the proportion of correct responses on T2 in each lag separately.

Finally, Raven's Advanced Progressive Matrices (RAPM; Raven, 1990) was administered to assess transfer to fluid intelligence.

Results

Comparisons between the training and the control group revealed a significant improvement of the training group in the dual *n*-back task, whereas the control group showed no change between the pre- and post-test assessments. With regard to the research question of transfer to executive functions, transfer occurred to three untrained measures: after training the trained participants reported more sequences correctly in the VS WM updating task, they showed decreased mixing costs in the task switching paradigm, and improved T2 detection in both the short and the long

lag of the AB task. These improvements exceeded the retest effect of the control group. There was no transfer found to the AV WM updating task, to the dual-modality WM updating task or to the PRP dual-task. There was also no transfer to fluid intelligence.

Discussion

Since transfer was observed to several tasks and since the tasks differed to a great extent from the trained material, one can exclude the possibility that training effects were purely stimulus- or task-specific. Transfer effect to the VS WM updating tasks implies that WM updating processes were improved, however, only in the visual modality. It might be that the auditory modality is generally more practiced in everyday life (due to e.g. speech perception and comprehension) that more extensive training would be needed for transfer effects. The improvements in the mixing costs of the task switching paradigm reflect improved processes of sustained control over items in WM; that is, in maintaining two task sets in WM and in selecting appropriately between them when task performance is required. Finally, the improvement in T2 detection in the AB task implies improved attentional control. However, as this effect was present over both lags, one cannot really conclude on the effect on AB itself (for that there should have been an effect only in the short lag). More specific inspection of the data revealed that AB might have been present still at the long lag, that is, that the long lag was too short for T2 to surpass the AB time window. As thus it is not quite clear which process the improvement in the AB task in this case reflects, one could speculate with an improvement in some attentional control processes after dual *n*-back training.

There was no transfer to the dual-task PRP paradigm and the RAPM. The lack of transfer to the PRP-task could be explained by a lack of commonalities between the tasks. The dual *n*-back training task essentially requires efficient updating of WM contents. This process is clearly not present in the transfer PRP dual-task. Instead, the dual-task of the PRP type requires fast processing and execution of appropriate stimulus-response mappings (Schubert, 1999, 2008), which is not an element in the training task. The lack of transfer to fluid intelligence (RAPM test) is in conflict with findings by Jaeggi et al. (2008, 2010), who found transfer to fluid intelligence after dual *n*-back training. There are, however, also other studies that have not been able to replicate the transfer effect from dual *n*-back training to fluid intelligence (Redick et al.,

2013). Therefore, there is no consensus on the possibilities to improve fluid intelligence with dual *n*-back training, and the findings from Study 1 rather support the view of no transfer.

In conclusion, the results showed that dual *n*-back training effects transferred to various tasks measuring executive functions: WM updating, maintenance and control over the material in WM (mixing costs in task switching), and attentional control processes (AB paradigm).

STUDY 2: WHAT ARE THE MECHANISMS OF TRANSFER?

Salminen, T., Kühn, S., Frensch, P. & Schubert, T. (submitted). Transfer after dual *n*-back training depends on striatal activation change.

Introduction

The second study was conducted in order to investigate the underlying mechanisms of dual *n*-back training and transfer effects. For this purpose I assessed training-related functional changes in the underlying neuronal substrate with fMRI. Neurofunctional parameters can provide more insight into the scope of commonalities and differences between the training and transfer tasks that may not be apparent on the behavioral level, such as activation of overlapping brain regions or activation changes in brain regions that are associated with shared cognitive processes.

Based on findings from previous studies, I formulated two hypotheses on the possible neuronal changes underlying training and transfer effects. The *general boosting hypothesis* predicts that transfer occurs whenever the general frontoparietal network is trained, and the transfer task relies on the same network. Methodologically transfer should occur whenever this overlap is present (Klingberg, 2010; Olesen et al., 2004). On the other hand, the *specific process improvements* hypothesis predicts that transfer requires that the training and transfer tasks engage the same specific cognitive processes. Additionally, the overlapping process should be observed as neuronal activation in the training and the transfer task in a brain region that is associated with that process. A previous study showed that transfer from visual WM updating training to a visual *n*-back task that also required WM updating was mediated by striatal activation (Dahlin, Stigsdotter Neely, et al., 2008). The striatum has been associated with WM updating (Baier et al., 2010; Frank et al., 2001; McNab & Klingberg, 2008) and therefore the transfer effect was likely due to an improvement in this specific process.

Considering the dual *n*-back, corresponding to Dahlin, Stigsdotter Neely, et al. (2008), a specific improved process could be WM updating, which is strongly involved in the task. In that case a strong candidate region for activation would be the striatum. One could also expect

an enhancement in dual-task processes, reflected as increased activation in the regions related to dual-task processing, such as the dlPFC (Schubert & Szameitat, 2003; Szameitat et al., 2002). On the other hand, the dual *n*-back task could be expected to boost the general frontoparietal network more strongly than the single visual WM task used in Dahlin, Stigsdotter Neely, et al. (2008) because of the increased involvement of executive processes. It is possible that a stronger involvement of that network leads to an increased boosting of the underlying neuronal functions. Consequently, increased boosting of the frontoparietal network could produce transfer to tasks that rely on the same network.

In order to test the two hypotheses, I investigated transfer from dual *n*-back training to WM updating tasks (analogous to the updating tasks in Study 1) that also required auditory and visual updating processes in single tasks and simultaneously in a dual-modality task. Importantly, the transfer tasks differed from the dual *n*-back task with respect to stimuli (black bars in four possible locations in the updating task vs. blue squares in eight possible locations in the *n*-back task; numbers one to four in the updating task vs. eight possible consonants in the *n*-back task) and the involved recalling processes (recollection of last presented items from WM in the updating task vs. recognition of a currently presented item in the *n*-back task). I also assessed transfer to single-modality versions (auditory and visual) of the *n*-back task. Therefore, all tasks included updating processes, but they differed with regard to stimuli and task rules. This way the tasks involved to varying degrees both overlapping and non-overlapping processes with the training task, and this allowed for specific assessment of the preconditions of transfer. If dual *n*-back training boosts a general cognitive ability, I anticipated (1) transfer from dual *n*-back training to all transfer tasks (WM updating transfer tasks: single- and dual-modality versions, as well as single *n*-back tasks), and (2) activation overlap in the frontoparietal network between the training and transfer tasks (and overlap should be decisive for transfer effects). But, if the dual *n*-back training exclusively improves a process that is very specific to the task, I would expect to see (1) no transfer, or alternatively limited transfer only to a task that mostly corresponds to the process engaged in the dual *n*-back task, that is the dual-modality version of the WM updating task. Transfer to single versions of the tasks would not be expected, because the participants specifically train to update the auditory and visual tasks simultaneously. In the

fMRI data I would expect (2) activation increase in a region associated with the specific process required by the two tasks. Corresponding to the findings by Dahlin, Stigsdotter Neely, et al. (2008), a strong candidate region is the striatum that is strongly involved in updating processes. Additionally, activation increase could be anticipated in the dlPFC which is associated with dual-task coordination processes.

Method

Eighteen participants (mean age 24.4 years; six male) trained on the dual *n*-back task for 16 sessions à 30 minutes across three weeks. As I was specifically interested in the significance of the unique complexity of the dual *n*-back task due to the dual task component, an active control group of 18 participants (mean age 24.1 years; four male) trained separately on the single subtasks of the dual *n*-back – that is, a single auditory-visual (AV) and a single visuospatial (VS) *n*-back task. A passive (no-contact) control group of 17 participants (mean age 25.0 years, seven male) did not undergo any training but attended only the pre- and post-test sessions (originally 18 participants took part in the passive control group, but due to technical failure in data collection, the data of one participant had to be discarded).

Before and after training participants performed in the MRI scanner the training dual *n*-back task as well as the transfer tasks: single *n*-back (AV and VS) as well as WM updating tasks (AV, VS, and dual-modality) that were described in detail in Study 1. The only exception to Study 1 was that in the dual WM updating task in Study 2 the participants were asked to report both the AV and the VS stimuli (whereas in Study 1 only one or the other was required). This way the dual WM updating resembled the dual *n*-back task more closely, since in the dual *n*-back the participants are also required to process both modalities simultaneously (rather than concentrating on one task stream while inhibiting the other).

In the fMRI data I assessed the first hypothesis (the general boosting hypothesis) with a conjunction analysis on the activations between the training [Contrast 1: (dual 2-back) – (dual 0-back)] and the transfer task [Contrast 2: (dual WM updating – baseline)]. Here, a voxel was reported active only when it was significant for both contrasts (Contrast 1 AND Contrast 2) (Nichols, Brett, Andersson, Wager, & Poline, 2005). The conjunction was calculated for each group, separately for pretest and posttest. If the first hypothesis holds, transfer should occur

when the training and transfer task activate overlapping regions in the general frontoparietal network.

For the second hypothesis (the specific process-improvements hypothesis) I examined activation changes (decreases and increases) in the training and the transfer task separately. In the training task, for decreases I calculated the contrast [(dual 2-back pre – dual 0-back pre) – (dual 2-back post – dual 0-back post)] and for increases the contrast [(dual 2-back post – dual 0-back post) – (dual 2-back pre – dual 0-back pre)]. For the transfer task the contrast for decreases was [(dual updating pre – baseline pre) – (dual updating post – baseline post)] and for increases [(dual updating post – baseline post) – (dual updating pre – baseline pre)]. If the second hypothesis holds, behavioral transfer effects should be accompanied by an activation increase in a specific brain region, the striatum, which is involved in updating processes. Additionally one could expect a dual-task related improvement. This possibility was approached by calculating contrasts for dual-task specific processes. I extracted activation related to dual-task coordination with the contrast [dual 2-back – (AV single 2-back + VS single 2-back)] (Schubert & Szameitat, 2003; Szameitat, Schubert, & Müller, 2011), separately for pretest and posttest. Subsequently, I analysed the change in dual-task related activation from pretest to posttest with the contrast [(dual-task contrast pretest – dual-task contrast posttest)] for decreased activation and with the contrast [(dual-task contrast posttest – dual-task contrast pretest)] for increased activation.

Results

The training group showed a significant improvement in the training dual *n*-back task, and moreover, there was a transfer effect to the dual WM updating task. However, there was no transfer to single versions in either the *n*-back task or the WM updating task. Although the trainees' performance improved from pretest to posttest in these tasks, a similar improvement was seen in the active control group in the single *n*-back tasks and the single WM updating tasks as well as in the passive control group in the single WM updating tasks. This implies that the improvements in those transfer tasks were not specific to dual *n*-back training. The active control group showed a significant improvement in the dual *n*-back task as compared with the passive control group; however, this effect was smaller than in the training group. This showed

that training of the subtasks of the dual *n*-back task separately as single tasks also improved performance to some extent, with dual *n*-back training still producing the broadest effects. Also, the improvement of the active control group in the dual *n*-back task did not transfer to the dual WM updating task.

With regard to the first hypothesis, the conjunction analyses on the tasks between which there was transfer (i.e., dual *n*-back task and dual WM updating task) revealed that *all* groups showed at pretest activation overlap between the two tasks in the general frontoparietal network, and notably, for the training group the amount of overlap was *smaller* at posttest than at pretest, especially in the frontal areas. In the active and passive control groups the overlap remained unchanged or became even larger than at pretest. According to the general boosting hypothesis overlap of neuronal activations in the training and transfer task should promote transfer. However, this was not the case: the training group - that is, the only group that showed transfer - had after training the least neuronal activation overlap between the training and the transfer task. Furthermore also the active control group that attended training with the single subtasks of the dual *n*-back showed initial overlap in the frontoparietal network, but not transfer to the dual WM updating task.

Regarding the second hypothesis, analyses of activation changes revealed in the training group an activation decrease in the general frontoparietal WM network in the dual *n*-back task, and an activation increase in the striatum in the transfer dual WM updating task. With a more lenient threshold a striatal activation increase was observed also in the training dual *n*-back task. The active control group showed frontoparietal activation decrease in the dual *n*-back task, but no activation changes in the transfer dual WM updating task. There were no activation changes in the passive control group in the dual *n*-back task or the dual WM updating task. The striatal activation increase in the training group supports the second hypothesis concerning enhanced task-specific processing, since the striatum is associated with WM updating processes.

To assess the relationship between neuronal activations and behavioral changes, the striatal activation changes from pretest to posttest in the training and transfer task were depicted for percent signal change values derived from region of interest analyses (ROI). These values were then correlated with the behavioral gain in the respective tasks (dual *n*-back and dual WM

updating). Visual inspection of the percent signal change data supported the finding from the whole-brain analyses of different activation patterns in the three groups: the training group showed an increase of the striatal percent signal change from pretest to posttest, whereas the control groups showed either no changes or rather a decrease. However, the correlation between the training group's percent signal change and behavioral gain was non-significant in both tasks. In order to gain an impression of a general association between striatal activation changes and behavioral changes, I compared the striatal percent signal change data between the lowest gaining participants across all three groups (15 % of participants who showed the *least* improvement from pretest to posttest, low gainers, $n = 7$) and the highest gaining participants across all three groups (15 % of participants who showed the *greatest* improvement from pretest to posttest, high gainers, $n = 9$). This analysis was performed for the dual *n*-back task and the dual WM updating task separately. In the dual *n*-back task there was a significant difference in the pretest-posttest comparison of the percent signal change between the lowest and highest gaining participants. In the dual WM updating task this difference was nearly significant. In other words, although the increase in the percent signal change could not be associated with training success, the striatal activation seems to be generally associated with performance.

Finally, in order to assess whether the performance improvements are due to improvements in dual-task coordination skills rather than WM processes, I analyzed dual-task specific activations. All groups showed decreased activation in brain regions associated with dual-task coordination processes (Schubert & Szameitat, 2003; Stelzel et al., 2008; Szameitat et al., 2002). As also the passive control group showed a decrease, it seems that pure task repetition produces changes in the neuronal substrate underlying dual-task coordination. The training group did not differ from the active or passive control groups in the amount or quality of change in dual-task related activations. This finding highlights that the observed performance improvements in the training group can be attributed to an improvement in specific WM processes and not to sole improvement of dual-task coordination skills.

Discussion

The results support the second hypothesis concerning the mechanism of transfer. That is, transfer occurs when the training and the transfer task engage a similar cognitive process. In

the neurofunctional data a shift seemed to occur in activation focus from the general frontoparietal network (decreased activation) to the striatum which is associated with WM updating processes (increased activation). Activation overlap in the general frontoparietal network was not sufficient for transfer. The present results are therefore in accordance with the findings from Dahlin, Stigsdotter Neely, et al. (2008), which showed transfer from WM updating training to an *n*-back task accompanied by an activation increase in the striatum. Also in their study, frontoparietal activation overlap was not sufficient for transfer, since they did not observe transfer to a Stroop task that activated overlapping frontoparietal regions with the WM updating task.

However the training and transfer tasks from Dahlin, Stigsdotter Neely, et al. (2008) were presented as single tasks only in the visual modality. The dual *n*-back task could be assumed to engage especially frontal regions stronger than a single-modality task, because the concurrent performance of the AV and the VS *n*-back tasks calls for executive task coordination processes that have in previous studies been located in the PFC (Miller & Cohen, 2001). The current results, thus, show that even a task that strongly activates the PFC does not boost the general cognitive functions that rely on the same network as the dual *n*-back task, but that a very specific process is improved. Dahlin, Stigsdotter Neely, et al. (2008) assessed transfer to an *n*-back task that can be considered to involve similar processes as their training updating task (WM updating); however, their other task, the Stroop task, measures inhibition of prepotent responses and therefore it does not show strongly overlapping processes with their training task. In the present study all tasks shared similar processes with the training task with only subtle deviations. One could, for example, expect dual *n*-back training to boost processes that are required in the single *n*-back tasks, especially as the same modalities (auditory and visual) are involved. However, this was not the case. The only transfer effect to the dual WM updating task implies that a very specific process was improved, and in this case the similar process involved in both tasks seems to be simultaneous WM updating of the two modalities.

The relationship between striatal activation increase and performance gain in the training and transfer tasks was supported by analyses that revealed the striatal activation increase to be larger in participants who showed the most behavioral gain compared with

participants who showed the least behavioral gain. Furthermore, specific analyses of activation changes related to dual-task coordination processes confirmed that the observed performance improvements could indeed be attributed to improved WM processes rather than improved dual-task coordination skills. A more elaborate discussion on the findings is placed in the General Discussion.

STUDY 3: CHANGES IN STRUCTURAL CONNECTIVITY AFTER DUAL *N*-BACK TRAINING

Salminen, T., Mårtensson, J., Kühn, S., & Schubert, T. (2016). Increased integrity of white matter pathways after dual *n*-back training. *NeuroImage, 133*, 244-250.

Introduction

In the third study I investigated changes in white matter microstructure after dual *n*-back training. Parameters of white matter microstructure are indicative concerning structural connections in the brain. A common assessment method is DTI that provides diverse parameters related to water diffusion in white matter.

Previous studies have shown that motor and musical training affect white matter connections between brain regions that are associated with the cognitive processes of the training task (Bengtsson et al., 2005; Scholz et al., 2009; Steele, Bailey, Zatorre, & Penhune, 2013). Mostly increased white matter integrity has been reflected as an increase in fractional anisotropy (FA), which is an indicator of the degree of anisotropy (directionally dependent diffusion) in white matter fibers. The larger the FA, the more there is water diffusion into one direction as compared with other directions, and thus, the more solid are the neuronal fiber connections. Only one study previous to now has studied white matter changes after WM training (but see also Lövdén, Bodammer, et al., 2010). Takeuchi et al. (2010) showed increased FA in frontal and parietal regions after visual *n*-back training. More specifically, the effects were found in white matter near the intraparietal sulcus, which is an essential node in the neuronal network for visuospatial WM (Todd & Marois, 2004), as well as in the genu of corpus callosum, which connects the left and right PFC and is therefore crucial for information transfer between frontal regions in the two hemispheres. Also the genu of corpus callosum is associated with WM performance so larger FA values are associated with better WM performance than lower FA values (Nagy et al., 2004). One limitation however of the Takeuchi et al. (2010) study is that the results were not compared against a control group, so it is difficult to dissociate true effects related to training from changes that take place with natural maturation. Furthermore training

included only the visual modality, which might explain why the effects were concentrated on brain regions that are associated with visuospatial WM processes. The dual *n*-back task could produce broader changes in white matter connections, as it involves two modalities (auditory and visual), and therefore it activates regions related to WM processes of both modalities. Also, it presumably engages frontal regions stronger than a single task because of the additional dual-task coordination component. Therefore, in the third study I examined dual *n*-back training-related changes that occur in white matter microstructure.

Although this study was rather explorative in nature, based on the previous WM intervention study (Takeuchi et al., 2010) and on studies that have associated WM performance with the microstructure of different white matter pathways (Charlton et al., 2010; Nagy et al., 2004; Olesen et al., 2003; Short et al., 2013), I hypothesized that dual *n*-back training would generate changes in white matter microstructure manifested as increased FA. However, as one previous study has reported a training-related decrease in FA (Taubert et al., 2010), also that possibility cannot be ruled out. I especially expected effects in regions that are connected with the frontal cortex. This is because the dual *n*-back task involves two different modalities (visual and auditory) that have both been shown to be associated with the frontal cortex. Additionally the dual-task characteristic of the task (i.e., simultaneous processing of the two tasks) calls for supplementary engagement of executive processes that are associated with the same region. Thus, strong activation of the neuronal structures during training should provoke changes in white matter pathways connecting the cortical regions that support WM. The pathways include connections between the left and right frontal lobes (the genu of corpus callosum), connections from the parietal and temporal lobes to the frontal lobe (the arcuate fasciculi), connections from the temporal lobes to the frontal lobes (the anterior cingulum), and thalamocortical white matter pathways.

Method

The participants in Study 3 were the same as in Study 2, with the inclusion of two additional training group participants in Study 3. They were excluded from Study 2 analyses because of differences in the response devices in the scanner. Because in Study 3 I did not analyze behavioral changes in the tasks that were performed in the scanner, or neurofunctional changes

that might be affected differently by the different devices, these participants could be included in the DTI analyses of Study 3. As in Study 2, participants were divided into three groups: a training group that trained on the dual *n*-back task (20 participants, mean age 24.2 years; six male), an active control group that trained on the single *n*-back tasks (18 participants, mean age 24.1 years; four male), and a passive control group that attended no training (18 participants, mean age 25.0 years, seven male; note that since behavioral data from the scanner was not analyzed for DTI, the passive control participant that was discarded due to data loss in Study 2 could be included in the analyses of Study 3). The training and the active control group trained on their respective training tasks for 16 sessions spanning over three weeks; the passive control group had no activities related to the study during this time. All groups attended before and after the training period an MRI-scanning session for DTI assessment. The measure for white matter microstructure was fractional anisotropy (FA). Additionally participants attended behavioral pre- and posttest sessions on separate days in order to assess possible behavioral changes in the dual *n*-back task in the control groups.

Results

The behavioral results were described in detail in Study 2. As a short recap, both the training group and the active control group improved significantly in their respective training tasks. Compared to the passive control group, the active control group also showed an improvement in the dual *n*-back task although they had trained on the single *n*-back versions of the dual *n*-back task. However, this improvement was significantly smaller than the improvement of the training group. The passive control group showed no change between pretest and posttest.

The DTI whole-brain analyses revealed that the training group showed increased FA from pretest to posttest in several white matter pathways, as compared to the active and passive control group. There were no differences between the active and passive control groups in their FA changes from pretest to posttest. In the comparison between the training group and the passive control group the FA results from the group (training vs. passive control) × time (pretest vs. posttest) interactions were almost brain-wide but primarily frontal and left hemispheric. The comparison between the training group and the active control group showed results from the group (training vs. active control) × time (pretest vs. posttest) interaction that were mainly left

hemispheric. More specifically, after dual *n*-back training, the training group showed increased FA in parts of five main white matter pathways: the superior and inferior longitudinal fasciculi, the inferior fronto-occipital fasciculus, the forceps minor, and the corticospinal tract. The superior longitudinal fasciculus connects the temporal and parietal lobes to the frontal lobe, the inferior longitudinal fasciculus connects the occipital and temporal lobes, the inferior fronto-occipital fasciculus connects the occipital and frontal lobes, and the forceps minor connects the lateral and medial surfaces of the left and the right frontal lobes via the genu of corpus callosum. In sum, dual *n*-back training seemed to increase microstructural white matter integrity in connections between several brain regions.

Next, the FA values were extracted in the pretest and posttest data for each participant covering all the regions in which significant effects were detected, thus resulting in one FA value per session and per participant. This was done in order to assess the relationship between microstructural changes and behaviour, that is, between the pretest to posttest change in FA and the pretest to posttest change scores in the dual *n*-back task. The correlation between the increase in FA and gain in the dual *n*-back task within the training group was not significant. Therefore, I analysed the general relationship between FA increase and dual *n*-back gain by correlating the pretest to posttest change in FA values and in the dual *n*-back task across all groups. This correlation was significant. That is, there was a general association between a change in FA and the gain in dual *n*-back task when all participants (training and control) are considered.

Discussion

The results demonstrate increased integrity in white matter connections (reflected as increased FA) between different brain regions after dual *n*-back training. According to previous studies I expected changes in the genu of corpus callosum, in the arcuate fasciculi, in the anterior cingulum, and in thalamocortical white matter pathways. The observed FA increase after dual *n*-back training occurred in the superior and inferior longitudinal fasciculi, the inferior fronto-occipital fasciculus and the forceps minor. The superior longitudinal fasciculus in the left hemisphere connects Broca's and Wernicke's areas, and is therefore associated with language processing (Catani et al., 2007; Catani, Jones, & ffytche, 2005). In left and right hemisphere it

connects the temporal and parietal lobes to the frontal lobe. The superior longitudinal fasciculus largely overlaps with the arcuate fasciculus as defined by Catani and Thiebaut de Schotten (2008). The forceps minor runs via the genu of corpus callosum and it connects the lateral and medial surfaces of the frontal lobes; therefore it plays a crucial role in interhemispheric communication in frontal areas. The increased FA in the superior longitudinal fasciculus and the forceps minor therefore corresponded to the white matter pathways in which FA increase was expected. However, changes in other pathways that were not predicted can be attributed to different characteristics of the training task. The inferior longitudinal fasciculus connects the temporal and occipital lobes and it engages in visual processing (ffytche & Catani, 2005), but also in WM (Nagy et al., 2004). The inferior fronto-occipital fasciculus connects the occipital and frontal lobes. Although its function is not clearly understood, some studies have attributed a role for it in visual processing (Fox, Iaria, & Barton, 2008).

These findings are in accordance with the results by Takeuchi et al. (2010), who found increased FA in a white matter region near the intraparietal sulcus as well as in the genu of corpus callosum; both of these regions are associated with WM performance, with the intraparietal sulcus being especially involved in visuospatial processing. The finding is in accordance with the visual modality of their training task. In the present study, dual *n*-back training seemed to produce more brain-wide effects than the visual training in Takeuchi et al. (2010): the current findings extended into connections that are associated also with auditory (language) processing. It is notable that the current findings were observed after only 16 training sessions à 30 minutes, whereas in Takeuchi et al. (2010) the minimum amount of training sessions over three months was 50, with a daily training time of approximately 25 minutes.

Both Takeuchi et al. (2010) and the current study have shown increased FA in the genu of corpus callosum. In the present study the FA increase in this region seemed to be more pronounced when the training group was compared with the passive control group than when it was compared with the active control group who trained the single component tasks of the dual *n*-back and thus required no multimodal integration. As increased FA here was observed also after visual WM training (Takeuchi et al., 2010), it is implied that increased connectivity

between the two hemispheres in the PFC reflects improved WM processes rather than improved multisensory integration.

However, only the simultaneous processing of auditory and visual WM tasks (as in the dual *n*-back) increased FA in connections that are associated with sensory-specific (auditory and visual) processing. This was shown in the results that showed increased FA in the connections in the training group when compared with the active control group. The results thus indicate that the crucial component of the training task in producing brain-wide effects in increased connectivity is its co-occurring bi-modality. If single-modality training produced similar effects in these regions, there should have been differences in FA changes from pretest to posttest between the active and passive control groups; however this was not the case.

There was limited evidence toward an association between the observed increases in FA and performance gain from pretest to posttest in the training task. Although there was no correlation between FA increase and training gain within the training group, there was an association between FA change and behavioural pretest to posttest change when all groups were considered. The non-significant correlation within the training group is similar to findings from a study on the effects of motor training on white matter microstructure, which was also not able to show a training-related relationship between behavioural gain and FA increase (Scholz et al., 2009; but see Taubert et al., 2010). Takeuchi et al. (2010) on their part did not correlate their FA changes to behaviour but to training time, and they found an association between the time spent for training and the increase in FA in parietal areas. It is therefore possible that the anatomical changes are more closely related to the amount of training in time rather than to training gain in performance.

In conclusion, in Study 3 I could show that only 16 sessions of dual *n*-back training increases the integrity of white matter connections between several brain regions. This is one of the first studies to show WM training-related changes in white matter microstructure, and the first study to show increased connectivity between brain regions after a relatively short period of WM training.

STUDY 4: WHAT ARE THE DUAL *N*-BACK TRAINING AND TRANSFER EFFECTS IN OLDER ADULTS?

Salminen, T., Frensch, P., Strobach, T., & Schubert, T. (2016). Age-specific differences of dual *n*-back training. *Aging, Neuropsychology, and Cognition, 23*(1), 18-39.

Introduction

In the fourth study I investigated the effects of dual *n*-back training in older adults. It is known that aging is accompanied by impairments in WM functions, and that these impairments might underlie – at least partially – general age-related cognitive decline for example in executive functions (Verhaeghen & Salthouse, 1997). Previous studies have provided mixed results on training and transfer effects in older adults, with some showing little or no transfer at all from training (e.g. Dahlin, Nyberg, et al., 2008), whereas some have shown broad transfer effects (e.g. Borella et al., 2010). The effects of dual *n*-back training in older adults have not yet been studied. Comparisons of performance differences between young and older adults have revealed that the differences increase as a function of task complexity, especially in dual-task situations (Jaeggi et al., 2009; Salthouse, 1992; Voelcker-Rehage et al., 2006). Therefore a complex training paradigm such as the dual *n*-back (that taps on both WM and dual-task processes) could be optimal in balancing out age-related differences in performance. Several studies have shown training-related improvements after dual *n*-back training in young adults (Jaeggi et al., 2008; Lilienthal et al., 2013) and in Study 1 of the present dissertation I showed transfer from dual *n*-back training to various executive functions in young adults.

In Study 4 I thus investigated dual *n*-back training effects and transfer to executive functions in older adults. The transfer tasks were the same as for young adults, with the exception that the dual WM updating task, the dual-task PRP paradigm, and the RAPM were excluded because they seemed too demanding for the older adults (dual WM updating) and / or there was no transfer effect observed in the young adults (dual WM updating, PRP, and RAPM). As transfer effects in older adults have in previous studies been generally restricted as compared with young adults (e.g. Brehmer et al., 2012; Dahlin, Nyberg, et al., 2008), it would be unlikely

to observe transfer in older adults to tasks to which there was no transfer observed in young adults. That is, in older adults the transfer tasks included the auditory-verbal (AV) and the visuospatial (VS) WM updating tasks, the task switching paradigm, and the attentional blink paradigm.

The most likely task for transfer effects would be the WM updating task, since the required processes mostly resemble those that are strongly engaged in the training task (WM updating). Considering that in Study 1 with young adults transfer occurred only to the VS version of the task and not to the AV version, this result pattern is most probable also in older adults. Additionally one could expect a transfer effect to the sustained control processes that are assessed in the mixing costs of the task switching paradigm. This is based on findings from a previous study that showed task switching training to improve especially these processes (but not general task switching abilities as measured in switch costs) in older adults (Karbach & Kray, 2009). Furthermore, in Study 1 with young adults a transfer effect from dual *n*-back training was found to mixing costs but not to switch costs. As for the AB task, in Study 1 the younger adults showed a transfer effect from dual *n*-back training to T2 detection. Although this effect was equal across the short and the long lag, and it therefore remains speculative whether the AB was reduced, the finding is likely to reflect some improvement in crossmodal attention processes. A previous study showed a decrease AB in older adults after meditation training (van Leeuwen, Müller, & Melloni, 2009). Thus, a transfer effect to the AB task could be expected in older adults after dual *n*-back training.

As I was specifically interested in age-related effects, I compared the training and transfer results of older adults with the training and transfer results of young adults from Study 1. Furthermore including the data from the young adults allowed a specific inspection of training-related compensation of age-related decline. This was possible by comparing the performance level that the older adults reached after training with the baseline level of the young adults before training. That is, if the older adults can after training perform on the same level as young adults before training, this would imply that training has been effective in compensating for age-related impairments concerning performance in that task.

Method

Twenty-six older adults (mean age 65.0 years, 11 male) attended 14 sessions of dual *n*-back training. Twenty-one older adults (mean age 65.1 years, eight male) were assigned to a passive control group that did not undergo training. The results of the older adults were compared to the data of the young adults from Study 1. The included tasks (dual *n*-back training paradigm, AV and VS WM updating task, task switching, and attentional blink) as well as the training schedule and study design were similar to the ones in Study 1.

Results

The results showed positive effects of dual *n*-back training in older adults. Compared to the passive control group, the older trainees significantly improved their performance in the dual *n*-back task from pretest to posttest. Although their training gain was smaller than that of young adults, at the end of training the older adults reached the baseline performance level of the young adults. That is, there were no performance differences at the end of training between the trained older adults and the untrained young adults. Moreover, there was a transfer effect to the VS WM updating task. This effect was again smaller than that observed in young adults, but, also here the posttest performance of the older adults was not significantly different from the pretest performance of the young adults. There were no other transfer effects observed.

Discussion

These results showed that dual *n*-back training can be used to train also older adults, and that only 14 sessions of training compensate for performance differences between young and older adults in WM tasks. Improvements did not, however, generalize as broadly in older adults as they did in young adults, since there was no transfer to the mixing costs in task switching or to the AB task. One possible cause for this could be that the training intervention was too short for the older adults. There are some discrepancies in the extent of transfer between training regimes of different lengths, with some short-term interventions showing broad transfer effects (e.g. Borella et al., 2010), whereas some long-term interventions have shown scarce transfer effects (e.g. S.-C. Li et al., 2008). However, Dahlin, Nyberg, et al. (2008) have highlighted that in addition to the relative training gain one should also consider the final performance level

reached after training when evaluating the extent of transfer. That is, a longer training intervention with the dual *n*-back task could allow the older adults to perform on a higher level of *n* at the end of training, which could possibly lead to broader transfer effects than the ones observed in Study 4. This remains to be investigated in future studies. In conclusion, although transfer effects were narrower than in young adults, the results from Study 4 showed that cognitive flexibility can be reached with the dual *n*-back training paradigm still at an older age.

GENERAL DISCUSSION

In this dissertation I investigated cognitive and neuronal effects and mechanisms of WM training in young adults. Additionally I studied the effects of WM training in older adults, and compared them with those of young adults in order to gain insight into the prospects of compensating for age-related cognitive decline by WM training. I especially focused on the effects of the dual *n*-back task that has previously been shown to produce broad transfer effects to untrained tasks. Additionally, the task is conceptually intriguing since it fulfills several requirements set upon successful cognitive training paradigms: it is challenging to the cognitive system and the level of difficulty can be easily adapted to match the participant's performance. Therefore the task embodies the potential to improve diverse cognitive abilities. The four specific research questions in my dissertation were:

1. Do WM training effects from dual *n*-back training transfer to executive functions? Several executive functions are involved in the dual *n*-back task: WM updating, coordination of two co-occurring tasks, and inhibition of irrelevant items. I investigated whether dual *n*-back training effects transfer to the executive functions that are engaged by the task.
2. What are the mechanisms of transfer to untrained tasks? Although theories have been developed to explain training and transfer effects, there is still no consensus on what predetermines transfer. I analyzed training-related changes in the neurofunctional activation patterns that could give insight into the mechanisms of training and transfer effects.
3. Does training produce changes in the neurostructural connections between brain regions that support WM processes? Changes in brain structure would be indicative of structural plasticity in the neuronal system rather than flexibility based on changes in neuronal functions in the existing neuronal structures.
4. What are the dual *n*-back training effects and transfer effects to executive functions in older adults? Here I compared training and transfer effects between older and young adults. Thus I analyzed whether dual *n*-back training could be applied as a WM training

paradigm in participants with WM impairments, and whether training effects transfer to executive control functions.

In the following I will discuss the findings of the four studies in light of these research questions.

DUAL *N*-BACK TRAINING AND TRANSFER EFFECTS REVISITED

The results of Study 1 show that dual *n*-back training produces improvements in tasks tapping on different executive functions. These functions are all recruited in the dual *n*-back task to some extent, including updating of items in WM and control over task-sets in WM as measured in the mixing costs of the task switching paradigm. Study 1 is the first study to systematically investigate dual *n*-back transfer effects to executive functions. Therefore, these findings extend previous studies that have shown transfer effects from dual *n*-back training to fluid intelligence, attention, and spatial visualization abilities (Jaeggi et al., 2008; Jaeggi, Buschkuehl, Perrig, & Meier, 2010; Lilienthal et al., 2013; Stephenson & Halpern, 2013). Although there are also results of no transfer from dual *n*-back training (Redick et al., 2013), the current state implies that performance in various tasks can be improved with dual *n*-back training.

The improvements are manifested not only on a behavioral level as better performance in untrained tasks, but also as changes in the underlying neuronal substrate, as shown in Studies 2 and 3. The neurofunctional findings from Study 2 firstly contribute to cognitive training literature by showing the pattern of neuronal activation changes after dual *n*-back training, which has not been studied so far. This pattern consisted of a mixture of activation decreases and increases that was similar to the pattern observed by Dahlin, Stigsdotter Neely, et al. (2008) in single visual WM updating training. The activation decrease in the general frontoparietal WM network that underlies several cognitive functions implies that this neuronal substrate had become functionally more efficient, since less activation was required after training than before training and at the same time performance improved. In the striatum, on the other hand, activation increased from pretest to posttest. The striatum is associated with WM updating processes (e.g. Alexander et al., 1986), and therefore it is indicated that dual *n*-back training, in which WM updating plays an essential role, strengthened the neuronal signals in this region.

The behavioral and neurofunctional findings strongly imply that some cognitive processes were enhanced and neuronal signals were adjusted accordingly. A later discussion on the mechanisms of transfer will elaborate more on these findings.

In addition to behavioral and neuronal activation changes, dual *n*-back training produced changes in white matter tracts connecting different brain regions (Study 3). These were manifested as increased FA from pretest to posttest in several white matter pathways. Such changes in neuronal structures can be considered as plasticity of the neuronal system in response to changing task demands (Lövdén, Bäckman, et al., 2010). The DTI results from Study 3 are in accordance with previous longitudinal learning studies showing training-related increases in white matter integrity, manifested as increased FA values (Scholz et al., 2009; Takeuchi et al., 2010). However, Study 3 of the current dissertation is pioneering in several aspects. It is the first study to show increased integrity after WM training in white matter connections *between* several brain regions. One earlier WM training study used a visual dual-process *n*-back training and found increased connectivity *within* the parietal cortex and in genu of the corpus callosum (Takeuchi et al., 2010). Furthermore, Study 3 is the first study to show such effects after a WM training intervention of only 16 sessions; whereas Takeuchi et al. (2010) showed changes after a much more extensive intervention than in Study 3, covering over 50 training sessions.

There are several possibilities on the cellular mechanisms underlying the increased FA in white matter, including fiber re-organization, myelination, and formation of new synapses (Zatorre et al., 2012). Such changes seem to be rather stable compared with other, more transient cellular changes (Kleim et al., 2007). A strong candidate for the observed changes is myelination (formation of new myelin). Myelin insulates neuronal axons and therefore enhances the transmission of neuronal signals. Myelination still occurs in adulthood (Benes, Turtle, Khan, & Farol, 1994; Nuñez, Nelson, Pych, Kim, & Juraska, 2000) and it is sensitive to experience through the lifespan (Markham & Greenough, 2004). Changes in myelination most likely take place due to changes in neuronal firing, which would be induced by continuous exposure to demanding WM requirements in the dual *n*-back task. The activation changes observed in Study 2 support this view. Considering the findings from Study 2 and 3, it is intriguing that between frontal and parietal areas, in which activation decreased after dual *n*-

back training, the integrity of the white matter pathways increased. Such a pattern might imply toward increased efficiency in neuronal signaling: as the connections between brain regions are more solid, less neuronal firing is required for successful performance. One could for example assume an initial increase in training-related neuronal activations, which would trigger myelination in white matter connections, which would again be followed by an activation decrease in the connected brain regions. Some studies have already shown an inverse u-shape pattern in activation changes associated with training (Hempel et al., 2004; Kühn et al., 2013). Whether this is due to microstructural changes in neuronal pathways remains an interesting hypothesis for future studies.

Dual *n*-back training improved performance also in older adults, as was shown in Study 4 for the first time. Furthermore, training effects in older adults transferred to an untrained VS WM updating task. There were no other transfer effects. A longer training intervention might be needed in the elderly to produce as broad transfer effects as in young adults. And indeed, Brehmer et al. (2012) showed broad transfer effects after 20-25 sessions of WM training across five weeks, which constitutes a more extensive training intervention than in Study 4. However, Heinzel et al. (2014) showed broad transfer effects in older adults already after 12 sessions of training, and also Borella et al. (2010) showed broad transfer after only three training sessions. S.-C. Li et al. (2008) again showed after 45 daily WM training sessions in older adults transfer only to untrained WM tasks but not to more complex tasks. It thus seems that there might be several factors contributing into the extent of training and transfer effects in older adults, including the spacing of training sessions and other similar parameters of the intervention (Lustig et al., 2009). Study 4 shows that although being a complex cognitive training task, the dual *n*-back can be used as a WM training intervention in older adults. Whether a longer training period produces improvements of other cognitive functions in older adults, as well, remains to be investigated in future studies.

It is especially noteworthy that only after 14 days of dual *n*-back training the older adults reached the baseline level of young adults in both the training and the visual WM updating transfer task. Also S.-C. Li et al. (2008) showed that older adults reached after training the baseline performance level of young adults; however, their training period was over three times

longer than the training period in Study 4 (45 and 14 sessions, respectively). Study 4 therefore shows that compensating for age-related decline is possible after only 14 training sessions, at least when it comes to processes that are strongly involved in the training task.

WHEN DOES TRANSFER OCCUR?

The most fundamental findings concerning this question come from Study 2. Comparing the neuronal activation patterns and changes in the training and the transfer task can bring insight into the mechanisms of transfer that might be overlooked by analyzing only behavioral data. The findings from Study 2 clearly show that activation overlap of two tasks in the modality-unspecific frontoparietal network is not sufficient to provoke transfer. This way they contradict the suggestions by Klingberg et al. (2005) and Olesen et al. (2004) who proposed that if this network is boosted in training and the transfer task relies on overlapping regions in that network, transfer should occur. Results from Study 2 of increased striatal activation after training are instead in line with the findings by Dahlin, Stigsdotter Neely, et al. (2008), who showed a transfer effect to a single visual *n*-back task from visual WM updating training and an accompanying activation increase in overlapping regions in the striatum. Also Dahlin, Stigsdotter Neely, et al. (2008) concluded that a common activation of the general frontoparietal network is not sufficient for transfer, since a Stroop task showed overlapping activations in the same network as the training task but there was no transfer between the two tasks. The findings from Study 2 show that even a task that presumably sets high demands on the general frontoparietal network does not boost the frontoparietal network to the extent that transfer would occur beyond tasks that share very similar specific processes. Specifically, whereas Dahlin, Stigsdotter Neely, et al. (2008) showed transfer to a task that was highly similar to the training task, and they showed no transfer to a task that largely required different cognitive processes than the training task, the results from Study 2 provide evidence toward the high degree of required similarities for transfer between tasks: all transfer tasks in Study 2 required updating, but transfer occurred only to the dual-modality task. The findings from Study 2 provide specification to the hypothesis of specific process improvements, in that I observed initial activation overlap in the striatum in all groups, but an activation increase in that region

and transfer only in the training group. Thus, it does not seem that initial overlap in the striatum is predictive of transfer (as one might suggest on the basis of the results by Dahlin, Stigsdotter Neely, et al., 2008), but rather, transfer requires a training-related increase in this region.

One could ask that if training improves only a very specific cognitive process, how to explain the broad transfer effects from previous studies and the transfer effects from Study 1 in the current dissertation? Concerning the latter, in Study 1 of the current dissertation participants showed transfer to mixing costs in the task switching paradigm and to Target 2 (T2) detection in the AB paradigm. If dual *n*-back training improves only specific WM updating processes, how did these improvements come about? Mixing costs in task switching are considered to reflect sustained control processes of maintaining task-sets in WM. It could be assumed that specifically WM updating processes are required when the participant selects the currently needed task set from WM. Suggestive findings of this have been reported in the case of switching between stimulus-response mappings: better WM updating performance in an *n*-back task predicts more efficient selection between relevant and irrelevant stimulus-response sets (Colzato, Zmigrod, & Hommel, 2013). Therefore, the observed improvement in mixing costs could theoretically come about from an improvement in WM updating processes. As for transfer to the AB paradigm, WM plays a role in the AB (Akyürek, Hommel, & Jolicœur, 2007). Concerning the requirement in the dual *n*-back and the AB task to control the input of items into WM as well as their temporal order, one could suggest that shared WM updating processes are involved in an AB task. In this way, improved WM updating processes might have contributed into the transfer effect to T2 detection in the AB paradigm.

As for transfer results from other dual *n*-back training studies, Jaeggi et al. (2008) have shown the broadest transfer effect to fluid intelligence. The authors proposed that transfer occurred because the dual *n*-back task and the intelligence test engage overlapping cognitive processes. In a later study, Jaeggi, Studer-Luethi, et al. (2010) showed a strong correlation between performance in the dual *n*-back task and fluid intelligence tests (RAPM and Bochumer Matrizentest, BOMAT). It is implied that these tests share a common processing component involving WM updating processes that enables transfer. However, while the transfer effect from dual *n*-back training to measures of fluid intelligence has been replicated in some studies

(Jaeggi, Studer-Luethi, et al., 2010; Stephenson & Halpern, 2013), the finding is still controversial. In Study 1 I observed no transfer to fluid intelligence (measured with RAPM), and also other studies have questioned the replicability of that finding (Chooi & Thompson, 2012; Redick et al., 2013; Thompson et al., 2013). Therefore it has not yet been conclusively established whether dual *n*-back training improves fluid intelligence. As it seems that mainly processes related to WM updating are trained in the dual *n*-back task, future studies should focus on assessing how these processes are involved in the tasks to which transfer from dual *n*-back training has also been shown, such as fluid intelligence and attention.

The finding of different transfer effects in young adults between Study 1 and Study 2 is puzzling. Why in Study 1 was there a transfer effect to the VS WM updating task and in Study 2 to the dual WM updating task? Some differences between the studies might resolve this discrepancy. Probably the strongest point is the difference between the dual WM updating tasks in the two studies. In Study 1, namely, the participants were required to report *either* the AV *or* the VS stimuli; it was unbeknownst to the participants, which ones they would have to report until they were asked. This way the participants had to memorize both stimuli streams but recall only one and inhibit the other. The dual *n*-back task does not require such a process but rather the maintenance of both streams active. The dual WM updating task in Study 2 required the recalling of *both* the AV *and* the VS stimuli, and this way the required processes were closely related to the ones required in the dual *n*-back task. In fact, the different transfer findings to the dual WM updating task in Study 1 strengthen the conclusion of Study 2, that dual *n*-back training improves WM updating of two *co-occurring* modalities. Why there was a transfer effect to the VS WM updating task in Study 1 but not in Study 2 is more problematic. There were some other differences between the two studies, such as the training time (in Study 1 training included 14 sessions while in Study 2 it included 16 sessions); furthermore, in Study 2 the transfer tasks were performed in the scanner whereas in Study 1 they were performed in the laboratory. In the scanner the participants could not see the response buttons, as the participants laid on their backs and the buttons were placed on their legs. In the laboratory environment the participants could perceive the response keys. Thus, different processes relating to visuo-motor

coordination might have been involved in the two test situations that could explain the differences in the transfer findings.

It is noteworthy that in Studies 1 and 4 the results of the training group were compared with participants that underwent no intervention, that is, a passive control group. There has been some criticism toward studies that compare training results with the retest performance of a passive control group (Morrison & Chein, 2011; Shipstead, Redick, & Engle, 2010). This is because participants who attend training might be more motivated and prone to show any effects as compared with passive control participants who come to the laboratory only for the pretest and posttest assessment. In other words, such comparisons cannot specify whether training effects can be attributed to true effects of the training paradigm or just any intervention *per se*. Therefore the effects should be compared against an active control group that also attends an intervention but that can be dissociated from the studied training effects. In Studies 1 and 4 the trained participants showed transfer to some tasks but not to others; if behavioral improvements were due to unspecific effects of motivation and to just taking part in an intervention (and not to improvements produced by the dual *n*-back task), one could have expected to observe transfer to the whole task battery. Furthermore, recent meta-analyses have shown that there are no differences between the results of studies that have used a passive control group and that have used an active control group (Au et al., 2015; Karbach & Verhaeghen, 2014). In Study 2 of the present dissertation there were some differences in the behavioral and neurofunctional findings between the active and passive control group, but these effects could still largely be dissociated from the effects observed in the training group. Finally, in Study 3 there was no difference in the microstructural changes from pretest to posttest between the active and the passive control groups. All these things considered, it is unlikely that the findings from Studies 1 and 4 suffered from the comparison with a passive instead of an active control group.

FUTURE DIRECTIONS

In the present dissertation I showed neurofunctional changes following dual *n*-back training in different brain regions. These changes were accompanied by microstructural changes in white matter pathways that connect brain regions related to WM. An intriguing direction for future

studies is to start unraveling the *functional* connectivity patterns in the underlying neuronal substrate, which might bring more insight into how the more solid white matter pathways after training are associated with the neuronal firing patterns in different brain regions. Together these findings can bring us closer to understanding the systematics of neuronal changes that underlie training-related performance improvements.

Also, recent insights into the relevance of so-called resting-state networks in understanding the functional organization of the brain could inspire studies approaching the role of resting-state activation patterns in cognitive training. Resting-state networks refer to synchronous neuronal activation patterns during rest, that is, when the participant is not performing a task. Studies have shown altered patterns in resting-state networks in different patient groups, including Alzheimer's disease (R. Li et al., 2013), schizophrenia (Venkataraman, Whitford, Westin, Golland, & Kubicki, 2012), as well as attention deficit hyperactivity disorder (Uddin et al., 2008). These clinical pathologies are all associated with WM impairments, with studies having already provided preliminary evidence in alleviating the symptoms with cognitive training (e.g. Hubacher et al., 2013; Klingberg et al., 2005; Sitzer, Twamley, & Jeste, 2006). Investigating the effects of WM training on functional connectivity in resting-state networks could in clinical settings provide important tools for diagnostics as well as in planning rehabilitation interventions. There exists already some approaches to this issue (Takeuchi et al., 2013). However, the studies of the current dissertation have shown that the dual *n*-back training paradigm can produce differential and stronger neuronal effects than other WM training paradigms tapping on a single modality, and therefore it would be of interest to study the specific effects of the dual *n*-back training paradigm.

CONCLUSIONS

In the present dissertation I presented that WM training with the dual *n*-back task produces cognitive improvements that can be observed as changes in neuronal functions and brain structure. The training-related improvements are associated with improvements in specific cognitive processes rather than with a general enhancement in cognitive abilities. Specific training improvements can, however, transfer to untrained tasks that share specific processes

with the training task. Furthermore, room for improvements is preserved into old age. I consider that in addition to the cognitive flexibility and structural plasticity that was shown in the current dissertation, stability is also an important characteristic of our brain: it implies that also changes that are detrimental do not transfer between processes and therefore, cognitive impairments in one process should remain restricted. The results of training-related behavioral improvements in young and older adults along with the evidence of the potential for functional and structural changes are valuable for interventions and applications concerning optimizing cognitive performance and compensating for cognitive impairments and decline.

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